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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BROOKS, David, P** [US/US]; GlaxoSmithKline, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US).

(74) Agent: **GIBSON, Mark**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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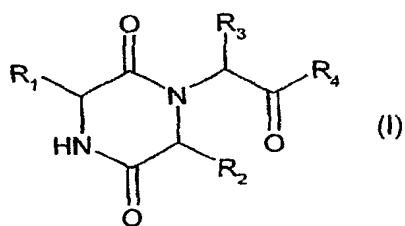
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(54) Title: SUBSTITUTED DIKETOPIPERAZINES FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA



(57) Abstract: A method of treating or preventing benign prostatic hyperplasia which comprises administering to a mammal in need thereof of an effective amount of a compound of Formula (I) where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are defined as provided in claim 1.

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## SUBSTITUED DIKETOPIPERAZINES FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

5 This invention relates to the use of a class of diketopiperazine derivatives having a potent and selective antagonism of oxytocin for use in the treatment of benign prostatic hyperplasia

USP5817751 describes combinatorial and solid phase methods for the synthesis of diverse diketopiperazine derivatives and the use of these methods to create libraries of diverse diketopiperazine derivatives.

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WO99/47549 describes diketopiperazine derivatives including 3-benzyl-2,5 diketopiperazine derivatives as inhibitors of fructose 1,6-bisphosphate (FBPase).

WO99/38844 describes a method for preparing N-[aliphatic or aromatic) carbonyl]-2-aminoacetamide compounds and their cyclisation to give inter alia diketopiperazine derivatives.

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WO99/37304 describes oxaheterocyclyl compounds including oxapiperazinyl compounds that are inhibitors of Factor Xa.

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Prostate oxytocin levels are raised in dogs with benign prostatic hyperplasia and this increase is associated with increased 5 alpha-reductase activity (Nicholson & Jenkin, 1995, Adv Exp Med Biol, 395, 529-538).

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Oxytocin stimulates prostatic growth in the rat (Popovic et al, 1982, Yugoslav Pharmacol Acta 18, 95-106).

Oxytocin is present in human prostate (Nicholson et al, 1985, J Endocrinol, 104 (Suppl) 127)

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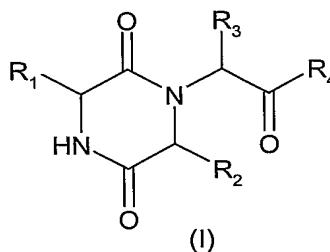
Oxytocin mRNA is present in the monkey prostate, suggesting local synthesis (Frayne & Nicholson, 1998, Molecular Human Reproduction. 4, 527-32)

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We have found a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor and thus are potentially useful in the treatment of benign prostatic hyperplasia

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The present invention thus a method of treating or preventing benign prostatic hyperplasia which comprises administering to a mammal in need thereof of an effective amount of an oxytocin receptor antagonist compound of the formula (I).



and/or a physiologically acceptable derivative thereof, wherein:

R<sub>1</sub> represents aryl (C<sub>1-4</sub>) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;

R<sub>2</sub> represents C<sub>1-6</sub>alkyl (optionally substituted by a C<sub>1-2</sub>alkoxy, C<sub>1-2</sub>alkylthio, di(C<sub>1-2</sub>alkyl) amino or a C<sub>3-6</sub> cycloalkyl group) or C<sub>3-6</sub>cycloalkyl, or 5-6 membered heterocyclic group containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;

R<sub>3</sub> represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene;

R<sub>4</sub> represents OH or OC<sub>1-4</sub> alkyl (optionally substituted with C<sub>1-4</sub>alkylcarbonyloxy) or NR<sub>5</sub>R<sub>6</sub>;

R<sub>5</sub> represents hydrogen, C<sub>1-6</sub>alkyl (optionally substituted with C<sub>1-4</sub>alkoxy) or C<sub>3-7</sub>cycloalkyl;

R<sub>6</sub> represents hydrogen, C<sub>1-4</sub>alkoxy, C<sub>3-7</sub>cycloalkyl, C<sub>1-4</sub>alkyl [optionally substituted with one or more groups selected from, carboxyl, C<sub>1-4</sub>alkylsulphonyl, or C<sub>1-4</sub>alkoxycarbonyl], C<sub>2-4</sub>alkyl [optionally substituted with one or more groups selected from halogen, hydroxy, C<sub>1-4</sub>alkoxy or NR<sub>7</sub>R<sub>8</sub> wherein R<sub>7</sub> and R<sub>8</sub> independently represent hydrogen or C<sub>1-4</sub>alkyl or together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from C<sub>1-3</sub>alkyl, hydroxy, C<sub>1-3</sub> alkoxy (optionally substituted by C<sub>3-6</sub> cycloalkyl or optionally substituted phenyl), C<sub>3-6</sub>cycloalkyl or NR<sub>c</sub>R<sub>d</sub> wherein R<sub>c</sub> and R<sub>d</sub> each independently represent a group selected from C<sub>1-3</sub>alkyl (optionally substituted by C<sub>3-6</sub> cycloalkyl or optionally substituted phenyl) or C<sub>3-6</sub> cycloalkyl)] or R<sub>6</sub> represents a phenyl or benzyl group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C<sub>3-7</sub> cycloalkyl or the group CH<sub>2</sub>CONR<sub>9</sub>R<sub>10</sub> wherein R<sub>9</sub> represents hydrogen or C<sub>1-4</sub>alkyl, R<sub>10</sub> represents hydrogen, C<sub>1-4</sub>alkyl optionally substituted by a 5 or 6 membered heteroaryl group or R<sub>9</sub>, R<sub>10</sub> and the nitrogen atom to which they are attached together form a 5 or 6 membered saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkanoyl group; or R<sub>5</sub>

and R<sub>6</sub> together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g. SO<sub>2</sub> and the additional nitrogen atom either carries a hydrogen atom or a C<sub>1-4</sub>alkyl or a C<sub>1-4</sub>alkanoyl group or a C<sub>1-4</sub>alkylsulphonyl group or a C<sub>1-3</sub>alkoxyC<sub>2-4</sub>alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from C<sub>1-3</sub>alkyl, hydroxy, oxo, C<sub>3-6</sub>cycloalkyl or NR<sub>e</sub>R<sub>f</sub> wherein R<sub>e</sub> and R<sub>f</sub> each independently represent a group selected from C<sub>1-3</sub>alkyl (optionally substituted by C<sub>3-6</sub>cycloalkyl or optionally substituted phenyl) or C<sub>3-6</sub>cycloalkyl].

A particularly useful class of compounds of formula (I) are those wherein R<sub>1</sub> is 2-indanyl optionally substituted by hydroxyl and more particularly a 2-indanyl group and R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> have the meanings defined above and/or physiologically acceptable derivatives thereof. A further useful class of novel compounds of formula (I) are those wherein R<sub>1</sub> is a 2-phenethyl and R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> have the meanings defined above and/or physiologically acceptable derivatives thereof.

The compounds of formula (I) contain at least three centers of asymmetry, namely the carbon atoms carrying the substituents R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> respectively and it is to be understood that formula (I) includes all possible stereoisomers and mixtures thereof. The substituent R<sub>3</sub> may exist in more than one tautomeric form and it is to be all understood that formula (I) includes all possible tautomeric forms and mixtures thereof.

The compounds of formula (I) wherein at least one of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> contains a basic or acidic grouping may form salts with physiologically acceptable acids or bases and reference to compounds of formula (I) herein includes such salts.

As used herein, the terms "physiologically acceptable derivative" or "pharmaceutically acceptable derivative", mean any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives are salts and solvates.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the

human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Examples of such esters include alkyl and 1-(acetyloxy)ethyl esters.

- 5 The term alkyl as a group or part of a group refers to a straight or branched alkyl group e.g. methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl, t-butyl, pentyl or hexyl.

- 10 The term C<sub>3-6</sub> cycloalkyl as a group or part of a group includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. The term C<sub>3-7</sub>cycloalkyl also includes cycloheptyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

- 15 Unless otherwise specified the term optionally substituted phenyl refers to a phenyl group which may be substituted by 1 to 3 substituents which may be the same or different and selected from halogen, hydroxy, C<sub>1-4</sub>alkyl (optionally substituted by 1-3 halogen atoms or NR<sub>g</sub>R<sub>h</sub> [wherein R<sub>g</sub> is hydrogen or C<sub>1-4</sub> alkyl, R<sub>h</sub> is hydrogen, C<sub>1-4</sub> alkyl, or R<sub>g</sub> and R<sub>h</sub> together with the nitrogen atom to which they are attached to form a 5 to 7 membered ring, which ring is saturated and may contain an additional heteroatom selected from
- 20 nitrogen, oxygen or sulphur]), C<sub>1-4</sub> alkylsulphonyl, carboxyl, C<sub>1-4</sub> alkoxy, carbonyl, di(C<sub>1-4</sub>alkyl)aminocarbonyloxy, C<sub>1-4</sub>alkoxy (optionally substituted by 1-3 halogen atoms, amino, C<sub>1-4</sub> alkylamino or di-(C<sub>1-4</sub>alkyl) amino), phenyl (optionally substituted by halogen or alkylaminosulphonyl), C<sub>1-4</sub>alkoxy, NR<sub>a</sub>R<sub>b</sub> [wherein R<sub>a</sub> is hydrogen or C<sub>1-4</sub> alkyl, R<sub>b</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkanoyl or C<sub>1-4</sub> alkylsulphonyl or R<sub>a</sub> and R<sub>b</sub>
- 25 together with the nitrogen atom to which they are attached to form a 5 to 7 membered ring, which ring is saturated and may be substituted by hydroxyl or 1 or 2 C<sub>1-4</sub>alkyl groups or may be spiro-fused to a dioxalane ring or may contain an additional heteroatom selected from nitrogen, oxygen or sulphur and may be substituted by 1 or 2 C<sub>1-4</sub>alkyl groups, or which ring is unsaturated and contains 1-3 additional nitrogen atoms], a 5 or 6
- 30 membered heteroaryl group, an optionally N-substituted aminocarbonyl or aminosulphonyl group (wherein the substituents may be 1 or 2 C<sub>1-4</sub> alkyl groups) or a dihydroxyboryl group).

- 35 The term 5 membered heteroaryl refers to a 5 membered ring which contains a heteroatom selected from oxygen, sulphur or nitrogen and which may also contain from 1 to 3 additional nitrogen atoms and which groups may be substituted by 1 or more groups selected from halogen, trifluoromethyl, C<sub>1-4</sub> alkyl, cycloalkyl, heteroaryl, saturated heterocyclic, or phenyl groups. Examples of such 5 membered heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl,
- 40 oxadiazolyl, thiadiazolyl, triazolyl or tetrazolyl and these heterocycles may be substituted as described above.

The term 6-membered heteroaryl group refers to a 6-membered unsaturated ring which contains from 1 to 3 nitrogen atoms and which may be substituted by 1 to 3 C<sub>1-4</sub> alkyl groups, or trifluoromethyl, or alkoxy groups. Examples of such groups include pyridyl, methylpyridyl, trifluoromethylpyridyl, pyrimidinyl and triazinyl.

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When R<sub>3</sub> is a 5 or 6 membered heteroaryl group this is linked to the rest of the molecule via a carbon atom in the ring.

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When R<sub>3</sub> is a fused bicyclic carbocyclic ring system this may be for example a naphthyl, tetrahydronaphthyl, indanyl or indenyl group.

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When R<sub>3</sub> is a fused bicyclic system containing up to 3 heteroatoms which may be the same or different, this is conveniently a 6,5 or 6,6 ring system wherein the heterocycle may be partially saturated or together with the benzene ring to which it is fused to form a heteroaryl group and the heterocycle may be substituted by 1 or 2 groups selected from C<sub>1-4</sub> alkyl or halogen or haloalkyl and or may contain a carbonyl group. The said R<sub>3</sub> group may be linked to the rest of the molecule via a carbon atom in the benzene ring or a carbon atom in the heterocyclic group.

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When R<sub>3</sub> is a fused 6,6 heteroaryl group the hetero ring contains from 1 to 3 nitrogen atoms and examples of such heteroaryl groups include quinoliny, isoquinoliny, phthalaziny, cinnoliny, quinazoliny, quinoxaliny, 1,2,3 benzotriazinyl or 1,2,4 benzotriazinyl.

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When R<sub>3</sub> is a 6,5 bicyclic heteroaryl group the 5 membered heterocycle contains a hetero atom selected from O, S or N and may in addition also contain a further 1 or 2 nitrogen atoms and the heterocyclic ring may also be substituted by 1 or 2 C<sub>1-4</sub> alkyl or halogen or haloalkyl and or may contain a carbonyl group. Examples of such 6, 5 bicyclic heteroaryl groups include benzofuranyl, benzothienyl, indolyl, benzo-oxadiazolyl,

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benzothiadiazolyl, benzo-oxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, benzimidazolyl, indazolyl or benzotriazolyl and these groups may be substituted as described above.

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When R<sub>3</sub> is a 6,6 or 6,5 bicyclic heterocyclic group and the heterocycle is partially saturated, this may contain 1 or 2 heteroatoms selected from O, S or N. Examples of such groups include indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothienyl, 1,3-benzodioxolyl, benzopyrrolyl, 1,3-benzodithiolyl 1,4-benzodioxanyl, phthalyl, thiophthalyl, chromanyl or chromenyl and the groups may be substituted by one or more halogen or C<sub>1-4</sub> alkyl groups, haloalkyl, or may contain a carbonyl group.

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When R<sub>3</sub> is a fused bicyclic heteroaryl linked via the benzene ring therein then suitable examples of such a group include 6-quinoliny, 4-isoindoliny, 4-(N-methyl-isoindoliny),

benzimidazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzimidazolyl  
benzoxazolyl, 2 methyl-benzo-oxazolyl, benzothiadiazolyl, benzotriazolyl and 1-methyl  
benzotriazolyl.

When R<sub>3</sub> is a fused bicyclic heteroaryl group linked via the heteroaryl ring this may be  
for example a 2-benzofuranyl, 2-benzothienyl or 2-N-methylindolyl group .

When R<sub>3</sub> is a 6,6 or 6,5 heterocyclic group wherein the heterocycle is partially saturated  
this is conveniently linked via the benzene ring therein and suitable examples include  
dihydrobenzofuran, dihydrobenzopyrrole, 1,3-benzodioxolyl, 2,2-difluoro-1,3-  
benzodioxolyl, and 1,4-benzodioxanyl.

When R<sub>3</sub> is a substituted phenyl group the said group conveniently carries from 1 to 3  
substituents which may be the same or different selected from fluorine, chlorine, bromine  
C<sub>1-3</sub>alkyl(methyl), C<sub>1-3</sub>haloalkyl (trifluoromethyl), C<sub>1-3</sub>alkoxy (methoxy, ethoxy),  
haloalkoxy (trifluoromethoxy), aminoethoxy e.g. dimethylaminoethoxy, C<sub>1-3</sub>  
alkoxycarbonyl, carboxy, hydroxy, phenyl or phenyl (substituted by halogen or  
alkylaminosulphonyl), NR<sub>a</sub>R<sub>b</sub> [wherein R<sub>a</sub> is hydrogen or C<sub>1-2</sub>alkyl and R<sub>b</sub> is C<sub>1-2</sub>alkyl,  
C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-3</sub>alkylaminocarbonyl] or NR<sub>a</sub>R<sub>b</sub> represents a  
pyrrolidino or piperidino ring, which ring may be substituted by a C<sub>1-2</sub>alkyl, hydroxyl or a  
2,2-1,3-dioxolane group or NR<sub>a</sub>R<sub>b</sub> represents a morpholino or a piperazino group which  
groups may be substituted by 1 or 2 C<sub>1-2</sub>alkyl groups or NR<sub>a</sub>R<sub>b</sub> represents a 5 or 6  
membered heteroaryl group containing from 1 to 4 nitrogen atoms (such as a 1-  
imidazolyl, 1,2-pyrazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl substituent), C<sub>1-3</sub>  
alkylsulphonyl, C<sub>1-3</sub>alkylaminocarbonyl, C<sub>1-3</sub>alkylaminosulphonyl, dihydroxyboryl or a  
5 or 6 membered atom heteroaryl group containing from 1 to 4 nitrogen atoms and which  
is linked to the phenyl group via a carbon atom in the heteroaryl group (for example  
pyridyl, pyrazolyl, imidazolyl or tetrazol 5-yl, which heteroaryl groups may be  
substituted by 1 or more C<sub>1-4</sub> alkyl groups.

Examples of suitable R<sub>3</sub> groups wherein R<sub>3</sub> is optionally substituted phenyl include  
phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-  
chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-  
difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-  
fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-  
3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-  
fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-  
fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-  
dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-  
morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-  
butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-  
chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-  
trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-  
methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-

methylaminocarbonylphenyl, 4-aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, 4-(1-3,5-di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4-t-butylthiazolyl)phenyl, 4-(5-2-t-butyltetrazolyl)phenyl, 4-(4-spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl or 3-(dihydroxyboryl)phenyl.

When R<sub>3</sub> is a 5 or 6 membered heteroaryl group suitable examples of such groups include 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-fluoro-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 2,3-dimethyl-5-thienyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-hydroxy-3-pyridyl, 6-methoxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, 4-oxazolyl, 4-thiazolyl, 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 4-isoxazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2-(4-morpholino)-5-thiazolyl or 2-(4-methyl-1-piperazino)-5-thiazolyl.

When R<sub>3</sub> is an optionally substituted fused bicyclic ring system examples of suitable groups include 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

When the group R<sub>1</sub> is a 5-7 membered cycloalkyl group which is fused to an optionally substituted benzene ring the optional substituents may be from 1 to 3 groups which may

be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

When the group  $R_1$  is aralkyl the aryl moiety is phenyl optionally substituted by 1 to 3 groups which may be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

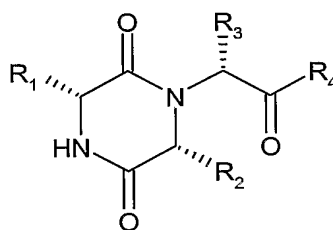
Examples of suitable  $R_1$  groups include phenethyl or indanyl optionally substituted by hydroxyl e.g. 2-indanyl, 1-hydroxy-2-indanyl, 5-hydroxy-2-indanyl.

Examples of suitable  $R_2$  groups include  $C_{3-4}$  alkyl e.g. isopropyl, 1-methylpropyl or 2-methylpropyl,  $C_{3-6}$  cycloalkyl e.g. cyclopentyl.

Conveniently  $R_4$  is hydroxy,  $C_{1-4}$  alkoxy e.g. methoxy, propoxy, t-butoxy, 1-acetyloxyethoxy or  $NR_5R_6$ .

A preferred class of compounds of formula (I) are those wherein  $R_4$  represents hydroxy or the group  $NR_5R_6$  or more preferably  $NR_5R_6$ .

A further preferred class of compounds is represented by formula (1a)



(1a)

wherein the groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  have the meanings defined for formula (I)

Conveniently  $R_1$  is a group selected from 2-phenethyl or 2-indanyl optionally substituted by hydroxyl and more particularly 2-indanyl. Conveniently  $R_2$  is a group selected from isopropyl, 1-methylpropyl, 2-methylpropyl or cyclopentyl and more preferably  $R_2$  is a group selected from 1-methylpropyl, or 2-methylpropyl.

Conveniently  $R_3$  is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-

carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-  
 dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-  
 methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-  
 methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-  
 5 methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-  
 methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-  
 pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-  
 imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-  
 dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-  
 10 acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-  
 N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-  
 (4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-  
 hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-  
 butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-  
 15 triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-  
 butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-  
 fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-  
 dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl,  
 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-  
 20 2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-  
 furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-  
 5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-  
 methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-  
 pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-  
 25 cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-  
 thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-  
 thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-  
 dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-  
 dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl,  
 30 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-  
 benzothiadiaazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-  
 benzofuran-5-yl, 1-methy-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-  
 indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-  
 1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-  
 35 benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-  
 benzimidazol-2-yl.

Conveniently the group R<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl e.g. methyl or C<sub>1-4</sub>alkoxyC<sub>2-4</sub>alkyl e.g.  
 2-methoxyethyl and R<sub>6</sub> is a group selected from hydrogen, C<sub>1-4</sub>alkoxy e.g. methoxy, C<sub>1-4</sub>  
 40 alkyl e.g. methyl, n-propyl, isopropyl or t-butyl, C<sub>1-4</sub> alkyl substituted by 1 to 3 halogen  
 atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C<sub>1-4</sub>alkyl substituted by alkoxycarbonyl or  
 carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g

methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroarylmethyl e.g. 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl  
 5 e.g. 2-1,3-thiazolyl, alkyl substituted by NR<sub>7</sub>R<sub>8</sub> [wherein NR<sub>7</sub>R<sub>8</sub> form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR<sub>5</sub>R<sub>6</sub> represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino, N-  
 10 methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

A preferred class of compounds are those of formula (1a) wherein R<sub>1</sub> is 2-indanyl, R<sub>2</sub> is a group selected from 1-methylpropyl or 2-methylpropyl and R<sub>4</sub> is hydroxy and/or more  
 15 particularly the group NR<sub>5</sub>R<sub>6</sub>.

A further preferred class of compounds are those of formula (1a) wherein R<sub>5</sub> is a group selected from hydrogen, C<sub>1-4</sub>alkyl e.g. methyl or C<sub>1-4</sub>alkoxyC<sub>2-4</sub>alkyl e.g. 2-methoxyethyl and R<sub>6</sub> is a group selected from hydrogen, C<sub>1-4</sub>alkoxy e.g. methoxy, C<sub>1-4</sub>alkyl e.g. methyl,  
 20 n-propyl, isopropyl or t-butyl, C<sub>1-4</sub> alkyl substituted by 1 to 3 halogen atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C<sub>1-4</sub>alkyl substituted by alkoxycarbonyl or carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g. methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzyloxyphenyl, dimethoxybenzyl,  
 25 optionally substituted heteroarylmethyl e.g. 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl e.g. 2-1,3-thiazolyl, alkyl substituted by NR<sub>7</sub>R<sub>8</sub> [wherein NR<sub>7</sub>R<sub>8</sub> form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR<sub>5</sub>R<sub>6</sub> represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino,  
 30 piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino, N-methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

35 A yet further preferred class of compounds are those of formula (1a) wherein R<sub>3</sub> is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2  
 40 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4

hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxy carbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiaazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methy-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

Particular preferred compounds for use in the invention include:

- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
- (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
- 5 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-morpholinamide
- (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.
- 10 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.
- 15 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
- 20 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- 25 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
- 30 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
- 35 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
- 40 (2R)-2-(2,4-difluorophenyl)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid

- methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- 5 1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-10 [(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione.
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione.
- 15 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide.
- 20 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide.
- 25 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione.
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
- 30 (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-2-(1,2,3-benzothiadiaazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- 35 (2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.
- 40 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.

- 5 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione.  
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide.  
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide.  
 10 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione.  
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide.  
 (2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.  
 15

The ability of the compounds of formula (I) to inhibit the actions of oxytocin may be determined using a variety of conventional procedures.

- 20 Thus, compounds of formula (I) have a high affinity for the oxytocin receptors on the uterus of rats and humans and this may be determined using conventional procedure. For example the affinity for the oxytocin receptors on the rat uterus may be determined by the procedure of Pettibone et al, Drug Development Research 30. 129-142 (1993). The compounds of the invention also exhibit high affinity at the human recombinant oxytocin  
 25 receptor in CHO cells and this may be conveniently demonstrated using the procedure described by Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p1301-1305.

- 30 The compounds of formula (I) are therefore useful in the treatment or prevention of benign prostatic hyperplasia.

- 35 The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt thereof for the manufacture of a medicament for treating benign prostatic hyperplasia

- 40 According to a further aspect, the invention also provides for a method for treating or preventing benign prostatic hyperplasia which comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

According to a further aspect, the invention also provides for a method for treating or preventing benign prostatic cancer which comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

5

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylactics as well as the treatment of benign prostatic hyperplasia and or benign prostatic cancer.

10 It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.

15

Thus for parenteral administration a daily dose will typically be in the range 2 to 50mg, preferably 5 to 25mg per day. For oral administration a daily dose will typically be within the range 10 to 800mg, e.g. 20 to 150 mg per day.

20 The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of formula (I) may be  
25 administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation for the treatment of benign prostatic hyperplasia comprising a compound of formula (I) or a pharmaceutically  
30 acceptable salt or non-toxic metabolically labile esters thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

35

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration.

40

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example,

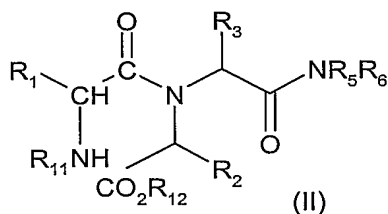
magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Compounds of formula (I) wherein  $R_4$  is the group  $NR_5R_6$  may be prepared by cyclisation of the compound of formula (II)



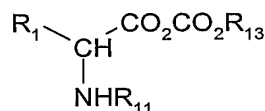
wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the meanings defined in formula (I) R<sub>11</sub> is hydrogen and R<sub>12</sub> is a C<sub>1-3</sub>alkyl group( e.g. methyl) in a suitable solvent such as an alkanol e.g. methanol and/or 2,2,2-trifluoroethanol, dioxan or a mixture thereof or a halohydrocarbon e.g. dichloromethane.

5

The compound of formula (II) wherein R<sub>11</sub> is hydrogen is conveniently prepared in-situ by treating a compound of formula (II) wherein R<sub>11</sub> is an acid labile nitrogen protecting group and R<sub>12</sub> is hydrogen or C<sub>1-3</sub>alkyl, with an acid in a suitable solvent followed by treatment with a hydrohalic acid and methanol if R<sub>12</sub> in the starting material is hydrogen, and then addition of a suitable base e.g. triethylamine or by treating a compound of formula (II) wherein R<sub>11</sub> is an hydrogenolysable nitrogen protecting group and R<sub>12</sub> is C<sub>1-3</sub>alkyl in a suitable solvent such as methanol or 2,2,2-trifluoroethanol with hydrogen in the presence of a suitable catalyst e.g. palladium on carbon.

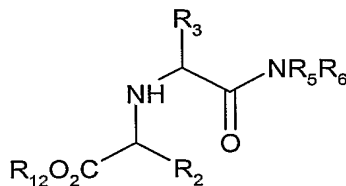
15 Examples of suitable nitrogen protecting groups  $R_{11}$  include alkoxycarbonyl e.g. t-butylloxycarbonyl or an optionally substituted benzyloxycarbonyl group.  
When  $R_{12}$  is  $C_{1-3}$ alkyl this is conveniently ethyl or more particularly methyl.  
Examples of a suitable acids include mineral acids such as hydrohalic acids e.g.  
hydrochloric acid or organic acids such as trifluoroacetic acid. The reaction is  
20 conveniently carried out in a solvent such as 1,4-dioxan or an alkanol e.g. methanol or a mixture thereof, or halohydrocarbon e.g. dichloromethane.

The compounds of formula (II) may be prepared by reaction of the mixed anhydride (III)



(111)

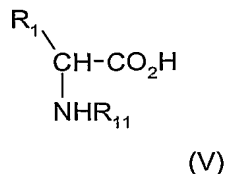
wherein R<sub>1</sub> and R<sub>11</sub> have the meanings defined above and wherein R<sub>13</sub> is a C<sub>1-6</sub> straight or branched chain alkyl, optionally substituted phenyl or benzyl group, with the amine (IV)



(IV)

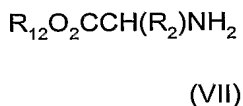
wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>6</sub> have the meanings defined above, and R<sub>12</sub> is hydrogen.

The reaction is preferably carried out in an aprotic solvent such as an ether e.g. tetrahydrofuran or a tertiary amide such as N, N-dimethylformamide or a mixture thereof. The compounds of formula (III) may be prepared by treating the N-protected amino acid (V)



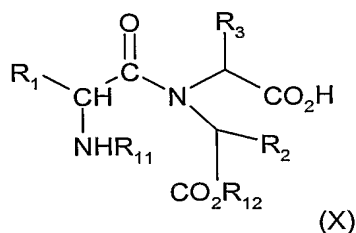
wherein  $R_1$  and  $R_{11}$  have the meanings defined above with the corresponding haloformate (VI;  $R_{13}CO_2X$  wherein  $R_{13}$  has the meaning defined in formula (III) and X is halogen e.g. chlorine, or bromine) in the presence of a suitable tertiary organic amine e.g. N-methylmorpholine and in an aprotic solvent e.g. an ether such as tetrahydrofuran or a hydrocarbon e.g. toluene.

The amine (IV) wherein  $R_5$  is hydrogen may be prepared treating the amino acid (VII)



wherein  $R_2$  has the meanings defined above and  $R_{12}$  is hydrogen with the aldehyde (VIII;  $R_3CHO$  wherein  $R_3$  has the meaning defined in formula (I)) in a suitable solvent such as an alkanol e.g. methanol followed by reaction with the isonitrile (IX;  $R_6N=C$  wherein  $R_6$  has the meanings defined in formula I other than hydrogen). Alternatively, the compounds of formula (II) wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meanings given in formula (I) and  $R_{11}$  is a nitrogen protecting group and  $R_{13}$  is a carboxyl protecting group may be prepared by reacting the amino acid derivative (VII) wherein  $R_2$  has the meaning given in formula (I) and  $R_{12}$  is a carboxyl protecting group with the aldehyde (VIII) wherein  $R_3$  has the meaning given in formula (I) in a solvent such as an alkanol e.g. methanol or 2,2,2-trifluoroethanol followed by the sequential addition of the amino acid (V) wherein  $R_1$  has the meanings given in formula (I) and  $R_{11}$  is a carboxyl protecting group and the isonitrile (IX) wherein  $R_6$  has the meanings given in formula (I).

Compounds of formula (II) wherein  $R_{12}$  is a  $C_{1-3}$ alkyl group may also be prepared by reacting the carboxylic acid (X) or an activated derivative thereof



wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_{11}$  have the meanings defined above and  $R_{12}$  is a  $C_{1-3}$ alkyl group, with the amine  $NHR_5R_6$  wherein  $R_5$  and  $R_6$  have the meanings defined in formula (I).

- 5 Examples of a suitable activated derivative of the carboxylic acid (X) include those commonly used in peptide synthesis e.g. that derived from reaction of benzotriazol-1-yloxytri-pyrrolidinophosphonium hexafluorophosphate in the presence of a suitable amine such as diisopropylethylamine.
- 10 The carboxylic acid (X) may be prepared from the corresponding compound of formula (II) wherein  $R_5$  represents hydrogen and  $R_6$  represents the 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.
- 15 Compounds of formula (II) wherein  $R_6$  represents 2-hydroxyphenyl are conveniently prepared by catalytic hydrogenolysis (e.g.  $Pd/H_2$ ) of the corresponding compound wherein  $R_6$  is a 2-benzyloxyphenyl group.
- 20 In a further aspect of the invention compounds of formula (I) as defined above may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein  $R_4$  is hydroxyl may be prepared from a compound of formula (I) wherein  $R_4$  is the group  $NR_5R_6$  and  $R_5$  is hydrogen  $R_6$  is 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent
- 25 reaction of the product thus formed with aqueous acetone.

Compounds of formula (I) wherein  $R_5$  is hydrogen and  $R_6$  is 2-hydroxyphenyl may be prepared from the corresponding compound of formula (I) wherein  $R_6$  is a 2-benzyloxyphenyl group by hydrogenolysis using hydrogen and a palladium catalyst.

- 30 Compounds of formula (I) wherein  $R_4$  is the group  $NR_5R_6$  may be prepared by reaction of the compound of formula (I) wherein  $R_4$  is hydroxyl or an activated derivative thereof with the amino  $NHR_5R_6$  wherein  $R_5$  and  $R_6$  have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine
- 35 such as  $NHR_5R_6$ .

Thus the amides may be prepared by treating the compound of formula (I) wherein  $R_4$  is hydroxyl with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) or oxalyl chloride in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed with the amine  $NHR_5R_6$ .

Alternatively compounds of formula (I) wherein  $R_4$  is the group  $NR_5R_6$  may be prepared by reacting a compound of formula (I) wherein  $R_5$  is hydrogen and  $R_6$  is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with the amine  $NHR_5R_6$ .

Compounds of formula (I) wherein  $R_4$  is  $OC_{1-4}$  alkyl (optionally substituted with  $C_{1-4}$ alkylcarbonyloxy) may be prepared by reacting the corresponding carboxylic acid ( $R_4$  is OH) or an activated derivative thereof with the appropriate alcohol ( $R_4OH$ ) or alkyl halide ( $R_4$ halide) under standard conditions for preparing such esters. Suitable activated derivatives include the acid halides, mixed anhydrides, those formed with coupling reagents commonly used in peptide synthesis e.g. carbonyldiimidazole and base salts of the acid e.g. alkali metal salts.

Compounds of formula (IV) may be converted into other compounds of formula (IV) using standard procedures. Thus compound of formula (IV) wherein  $R_5$  is hydrogen and  $R_6$  is 2-benzyloxyphenyl may be converted into other compounds of formula (IV) wherein  $R_5$  and  $R_6$  have other meanings as defined in formula (I) using the same procedures as described above for carrying out analogous reactions on compounds of formula (I).

Compounds of formula (I) wherein the stereochemistry of any of the substituents  $R_1$ ,  $R_2$  and  $R_3$  is as shown in formula (1a) may be prepared starting from the corresponding single isomers of the intermediates (III), (IV) and (VII) and/or the various isomeric mixtures may be separated by conventional procedures.

The intermediates (V), (VI), (VII), (VIII) and (IX) are either known compounds may be prepared by analogous methods to those known for preparing structurally related compounds.

Compounds of formula group (I) wherein  $R_4$  is OH may be prepared by cyclisation of a corresponding compound of formula (II) under the conditions described above for preparing compounds of formula (I).

Physiologically acceptable salts of a compound of formula (I) wherein R<sub>4</sub> is OH or one of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or NR<sub>4</sub>R<sub>5</sub> has a basic or acidic centre may be prepared by treating the said base or acid with the required physiologically acceptable acid or base and this reaction is conveniently carried out in a solvent for the said compound of formula (I).

- 5 Physiologically acceptable derivatives of a compound of formula (I) may be prepared from the appropriate intermediate corresponding to formula (II) using the process described above for preparing compounds of formula (I) or directly from the compounds of formula (I) by conventional procedures for preparing such derivatives. Thus metabolically labile esters may be prepared by esterification of the free carboxyl or  
10 hydroxyl group using standard esterification techniques.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

### 15 **General purification and analytical methods**

- Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO<sub>2</sub>H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO<sub>2</sub>H 5% water in acetonitrile (solvent B), using the following elution  
20 gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 0%B at a flow rate of 3 ml/minute. The mass spectra (MS) were recorded on a Fisons VG Platform spectrometer using electrospray positive [(ES+ve to give MH<sup>+</sup> and M(NH<sub>4</sub>)<sup>+</sup> molecular ions] or electrospray negative [(ES-ve to give (M-H)<sup>-</sup> molecular ion] modes on a Micromass series 2 or a Waters ZQ mass spectrometer. <sup>1</sup>H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the  
25 external standard. Biotage<sup>TM</sup> chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil. Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5μm column (5cmx10mm i.d.) with 0.1% HCO<sub>2</sub>H in water and 95% MeCN, 5% water (0.5% HCO<sub>2</sub>H)  
30 utilising gradient elution at a flow rate of 8ml minutes<sup>-1</sup>. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

- Hydrophobic frits refer to filtration tubes sold by Whatman. SPE (solid phase extraction)  
35 refers to the use of cartridges sold by International Sorbent Technology Ltd. TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F<sub>254</sub>. Oasis<sup>TM</sup> refers to Waters<sup>®</sup> Oasis<sup>TM</sup> HLB Extraction Cartridges, sold by Waters Corporation<sup>®</sup>.

**Method 1****Example 1**

(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

- To a solution of (D)-leucine methyl ester hydrochloride (300mg) in methanol (4ml) was added triethylamine (230  $\mu$ l) and 4-fluorobenzaldehyde (177 $\mu$ l). The mixture was stirred for 2.5 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (481mg) and isopropylisocyanide (225 $\mu$ l) were sequentially added. After stirring for 16hr, the solvent was removed *in vacuo* and the residue was dissolved in chloroform. This solution was washed with a saturated aqueous sodium carbonate solution (x2), aqueous citric acid (0.5M, x2) and brine (x1), dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in dichloromethane (2ml) and trifluoroacetic acid (5ml) and stirred for 3 hours at ambient temperature. After this time, the solvent was removed *in vacuo* and the residue co-evaporated with toluene (x3) and cyclohexane/ ether (1:1, x2). The residue was treated with a solution of triethylamine in dioxane (2% solution, 10ml) and was left to stir overnight. After this time, the dioxane was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with citric acid solution (0.5M, x2), saturated aqueous sodium bicarbonate solution (x1) and brine (x1). The liquors were then dried over magnesium sulphate and *in vacuo* and were then co-evaporated with cyclohexane: ether (1:1, x2). This crude material was purified by Biotage<sup>TM</sup> (90g, silica) eluting with toluene: ethyl acetate: cyclohexane (5: 3: 2) with 5% triethylamine to give (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide (149mg)
- HPLC Rt = 3.42 minutes; m/z [M+H]<sup>+</sup> = 480.
- <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.44 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H), 7.11 (t, 2H), 6.50 (d, 1H), 5.60 (d, 1H), 5.11 (s, 1H), 4.10 (m, 1H), 3.96 (m, 2H), 3.16 (dd, 1H), 3.07 (d, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.42 (m, 1H), 1.13 (d, 3H), 1.12 (d, 3H), 0.84 (d, 3H), 0.79 (d, 3H)

Similarly prepared

**Example 2**

(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.

- HPLC Rt = 3.27 minutes; m/z [M+H]<sup>+</sup> = 575.
- (CDCl<sub>3</sub>)  $\delta$  7.3 (d, 2H), 7.2 (m, 2H), 7.15 (m, 2H), 6.9 (d, 2H), 6.1 (d, 1H), 5.5 (s, 1H), 5.15 (s, 1H), 3.95 (m, 2H), 3.9 (m, 1H), 3.6 (m, 2H), 3.15 (m, 1H), 3.1 (m, 2H), 3.0 (m, 2H), 2.9 (m, 1H), 2.75 (m, 1H), 2.0 (m, 2H), 1.75 (m, 1H), 1.65 (m, 3H), 1.45 (m, 1H), 1.3 (s, 9H), 0.8 (d, 3H), 0.7 (d, 3H).

**Example 3**

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z [M+H]<sup>+</sup> = 565

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.52 (t, 1H), 7.22-7.11 (m, 4H), 7.04 (br s, 1H), 6.66 (dd, 1H), 6.56 (dd, 1H), 5.07 (s, 1H), 4.19-4.08 (m, 2H), 3.98 (dd, 1H), 3.86-3.81 (4H, m), 3.21-2.91 (m, 8H), 2.80-2.73 (m, 1H), 1.96-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (d, 3H), 1.16 (d, 3H), 1.06 (d, 3H), 0.92 (t, 3H).

10

**Method 2****Example 4**

- 15 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

Methyl (2R)-2-[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate

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- A mixture of 4-fluorobenzaldehyde (1.2g), (D)-leucine methyl ester hydrochloride (1.7g), triethylamine and methanol (56ml) was stirred at room temperature for 3 hours. 2-Benzyloxyphenylisocyanide (2.0g) and N-tert-butoxycarbonyl-(D)-indanyl glycine (2.77g) were then added sequentially. After 40 hours the reaction mixture was partitioned between 2M hydrochloric acid and ethyl acetate. The separated organic layer was washed with a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated *in vacuo*. The resultant crude material was purified by column chromatography (eluting with 0.5% and 0.2% methanol/ dichloromethane) to afford methyl (2R)-2-[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (4.3g)
- 25  
30  
HPLC Rt = 4.34 minutes, m/z [M+H]<sup>+</sup> = 752

- 35 Methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate

- A mixture of methyl (2R)-2-[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (560mg), palladium on carbon (70mg) and ethanol (15ml) was stirred under an atmosphere of hydrogen for 5 hours. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane
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(10% to 15%) to give methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate.

5 HPLC Rt = 4.06 minutes, m/z [M+H]<sup>+</sup> = 662

(2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid.

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Carbonyldiimidazole (558mg) was added to a solution of methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate (2.0g) in dichloromethane (20ml) and the resultant mixture was stirred at room temperature for 24 hours. The reaction was then concentrated to dryness, dissolved in a mixture of acetone: water (60ml: 40ml) and stirred for 17 hours at room temperature. The solution was then partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The separated organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. Half of the material was taken to be used crude in further experiments. The second half was purified by Biotage<sup>TM</sup> (silica, 90g) eluting with methanol: dichloromethane: ammonia (1: 98.5: 0.5 to 2.5: 86.5: 1). Evaporation of the appropriate fractions gave (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid. (173mg).

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25 HPLC Rt = 3.91 minutes, m/z [M+H]<sup>+</sup> = 571

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

A solution of (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid (73mg) in N,N-dimethylformamide (2ml) was sequentially treated with diisopropylethylamine (51μl), phosphorus<sup>I</sup> (1-hydroxy-1H-benzotriazolato-O)tri-1-pyrrolidinyl-(T-4)-hexafluorophosphate (80mg) and then after 2 minutes, 2,2,2-trifluoroethylamine (25μl). This reaction mixture was stirred for 2 hours before being partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane and stirred for 7 hours at room temperature. The reagent was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The separated organic fraction was washed with brine before being dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography (silica) eluting with

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methanol: dichloromethane (1% to 3%) to furnish ((2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide (10mg)

HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 520

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42 (m, 2H), 7.34 (d, 1H), 7.20-7.10 (m, 6H), 6.61 (t, 1H), 5.28 (s, 1H), 4.08-3.96 (m, 3H), 3.88 (m, 1H), 3.14 (dd, 1H), 3.02 (m, 2H), 2.95-2.77 (m, 2H), 1.88-1.70 (m, 2H), 1.40 (ddd, 1H), 0.85 (d, 3H), 0.79 (d, 3H).

The following compounds were prepared in a similar manner

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#### Example 5

((2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

HPLC Rt = 3.37minutes, m/z [M+H]<sup>+</sup> = 466

- 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>); δ 7.47-7.40 (m, 2H), 7.25-7.12 (m, 6H), 6.50 (d, 1H), 6.47 (s, 1H), 4.15 (dd, 1H), 3.98 (dd, 1H), 3.21-3.01 (m, 3H), 2.99 (s, 3H), 2.92-2.73 (m, 2H), 2.83 (m, 3H), 1.59-1.49 (m, 1H), 1.42 (dt, 1H), 0.66-0.57 (m, 1H), 0.62 (d, 3H), 0.40 (d, 3H).

#### Example 6

- 20 ((2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-morpholinamide

HPLC Rt = 3.32 minutes, m/z [M+H]<sup>+</sup> = 508

- 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>); δ 7.44-7.39 (m, 2H), 7.26-7.12 (m, 6H), 6.87 (d, 1H), 6.51 (s, 1H), 4.12 (dd, 1H), 4.00 (dd, 1H), 3.73-3.62 (m, 3H), 3.60-3.54 (m, 2H), 3.37 (m, 1H), 3.23 (m, 1H), 3.20-3.02 (m, 4H), 2.91-2.75 (m, 2H), 1.60-1.50 (m, 1H), 1.45 (dt, 1H), 0.63 (d, 3H), 0.62-0.55 (m, 1H), 0.42 (d, 3H).

The 2-fluoro-4-(morpholino)-benzaldehyde used in this synthesis was prepared by the following procedure.

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#### 2-Fluoro-4-(morpholino)-benzonitrile

A solution of 2,4-difluorobenzonitrile (6.03g, 43.35mmol) and morpholine (8.3ml, 95.17mmol) in tetrahydrofuran (27ml) was stirred at room temperature for 24hr. The mixture was evaporated and the white solid purified by Biotage<sup>TM</sup> column (90g, silica)

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eluting with cyclohexane: ethyl acetate: (4: 1) to give 2-fluoro-4-(morpholino)-benzonitrile as a white solid (5.81g, 65%).

HPLC Rt = 2.83 minutes; m/z [M+H]<sup>+</sup> = 207.

#### 2-Fluoro-4-(morpholino)-benzaldehyde

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To a solution of 2-fluoro-4-(morpholino)-benzonitrile (2.82g, 13.7mmol) in tetrahydrofuran (27ml) under a nitrogen atmosphere was added dropwise a 1.5 M solution of DIBAL-H in toluene (18.3ml, 27.3mmol) during 13minutes and the resulting mixture

stirred for 23.5hr at room temperature. The mixture was cooled to -50 °C and the excess DIBAL-H destroyed by careful addition of methanol (27ml). The mixture was then stirred at room temperature for 10 mins, saturated ammonium chloride (27ml) added and the resulting mixture stirred at room temperature for 40 mins., and then evaporated under reduced pressure to a yellow solid. This solid was partitioned between dichloromethane (120ml) and water (120ml) and solid potassium carbonate added until the aqueous phase was pH10. The phases were separated via a hydrophobic frit and the organic phase evaporated and the residue purified by a Biotage<sup>TM</sup> column (40g, silica) eluting with cyclohexane: ethyl acetate: (7:3) to give 2-fluoro-4-(morpholino)-benzaldehyde (1.96g, 68%) as a white solid.  
HPLC Rt = 2.63 minutes; m/z [M+H]<sup>+</sup> = 210.

### Method 3

#### Example 7

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

Methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate

To a stirred suspension of (L)-Leucine (1.3g) in methanol (100ml) under a nitrogen atmosphere was added 2,4-difluorobenzaldehyde (1.42g). After stirring at ambient temperature for 3 days, the suspension was cooled to -30°C and a solution of isopropylisocyanide (0.691g) in methanol (5ml) was added. After 3 hours at -30°C the reaction was allowed to warm to room temperature and was stirred for a further 20 hours. The solvent was removed *in vacuo*, the residue purified using a Biotage<sup>TM</sup> column (40g, silica) eluting with cyclohexane: ethyl acetate (gradient from 8:1 to 1:1). The required fractions were combined and concentrated *in vacuo* to furnish methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.326g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 (m, 1H), 6.88 (m, 1H), 6.82 (m, 1H), 6.78 (m, 1H), 4.42 (s, 1H), 4.07 (m, 1H), 3.69 (s, 3H), 3.18 (t, 1H), 1.66 (m, 1H), 1.49 (t, 2H), 1.18 (d, 3H), 1.15 (d, 3H), 0.88 (d, 3H), 0.77 (d, 3H)

N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.32g) in methanol (15ml) was added a solution of lithium hydroxide (294mg) in water (15ml). The reaction was rapidly stirred for 1.5 hours and then evaporated *in vacuo*. The residue was dissolved in water and neutralised using 2N hydrochloric acid. The resulting solid was collected by filtration and dried *in vacuo*. The filtrate was applied to 4 Oasis cartridges (6g), which were eluted with water (x2) and methanol (x2). The required fractions were combined and concentrated *in vacuo* to afford

N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (1.01g).  
HPLC Rt = 2.51 minutes; m/z [M+H]<sup>+</sup> = 343.

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (291mg) in dry tetrahydrofuran (5ml) under a nitrogen atmosphere at -20°C was added N-methylmorpholine (101mg) and a solution of isopropylchloroformate in toluene (1.0M, 1ml). After 10 minutes, a solution of N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (342mg) in N,N-dimethylformamide/tetrahydrofuran (5ml/ 10ml) was added and the resultant mixture was stirred at room temperature for 4 hours. The solvent was then removed *in vacuo* and the residue was treated with 4N hydrochloric acid in dioxane (2ml). After 4 hours, methanol (5ml) was added to the reaction mixture and this was left to stand for 18 hours. The solvent was then removed *in vacuo* and the residue was purified on an SPE cartridge (50g, silica) eluting with cyclohexane/ ethyl acetate (gradient from 4:1 to neat ethyl acetate), which furnished the two diastereomers as white solids (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide; (0.137g)

HPLC Rt = 3.47 minutes, m/z [M+H]<sup>+</sup> = 498  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.68 (m, 1H), 7.21 (m, 2H), 7.17 (m, 2H), 6.95 (m, 1H), 6.89 (m, 1H), 6.79 (d, 1H), 5.91 (d, 1H), 5.33 (s, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.92 (dd, 1H), 3.16 (m, 1H), 3.05 (m, 2H), 2.90 (m, 1H), 2.78 (m, 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 1.17 (m, 6H), 0.88 (d, 3H), 0.82 (d, 3H)

#### Method 4

#### Example 8

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate

To a suspension of L-leucine (2.33g) in methanol (200ml) at -30°C under nitrogen was added a solution of 2,4-difluorobenzaldehyde (2.52g) in methanol (10ml) and a suspension of 2-benzyloxyphenylisonitrile (3.7g) in methanol (40ml). The reaction was stirred at -30°C for 2.5 hours and then allowed to warm to room temperature and stirred for a further 6 days. The solvent was removed *in vacuo* and the residue was passed through a Biotage<sup>TM</sup> column (90g) eluting with cyclohexane: ethyl acetate (8:1 and 7:1) to afford after evaporation of the appropriate fractions methyl N-[(1R)-2-{[2-

(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (5.06g).  
HPLC Rt=4.0 minutes, m/z [M-H]<sup>-</sup> = 495

5 Methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate

A mixture of palladium on carbon (10%, 300mg), methyl N-[(1R)-2-{2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (2.88g) and ethyl acetate (30ml) was stirred under a hydrogen atmosphere for 3 hours. The reaction  
10 was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (2.179g).  
HPLC Rt=3.52 min, m/z [M-H]<sup>-</sup> = 405

15 Methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

A solution of methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (203mg) and 1,1'-thiocarbonyldiimidazole (100mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (10ml) was added to the  
20 reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide (TBTU, 321mg) and a solution of dimethylamine in tetrahydrofuran (0.5ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was  
25 then passed down an SPE (5g, silica) eluting with a gradient (8:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg).  
HPLC Rt = 3.16 minutes m/z [M+H]<sup>+</sup> = 343

30 N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg) in methanol (3ml) was added a solution of lithium hydroxide (15.4mg) in water (1ml). After stirring vigorously for 4 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid.  
35 This solution was applied to an Oasis<sup>TM</sup> cartridge (6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg).  
HPLC Rt = 2.23 minutes m/z [M+H]<sup>+</sup> = 329

40 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (84mg) in dry tetrahydrofuran (6ml) at  $-20^{\circ}\text{C}$  under a nitrogen atmosphere was added N-methylmorpholine (32  $\mu\text{l}$ ) and a solution of isopropylchloroformate in toluene (1.0M, 290  $\mu\text{l}$ ). After 10 minutes, a solution of N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg) in tetrahydrofuran (10ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (5ml) was added and the reaction was left to stand for a further 18 hours. The solvent was then removed *in vacuo* and the residue was dissolved in dioxan (5ml) and to this was added triethylamine (0.5ml). After 1 hour, the solvent was removed and the residue was applied to an SPE (10g, silica). The product was eluted using methanol. A second SPE was used to further purify the material (2g, silica) using an ethyl acetate: methanol gradient (20:1 to 1:1) to afford (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (38mg).

HPLC  $R_t$ =3.5 minutes,  $m/z$   $[M+H]^+ = 484$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.42 (m, 1H), 7.22 (m, 2H), 7.17 (m, 2H), 7.02-6.90 (m, 2H), 6.62 (s, 1H), 6.37 (m, 1H), 4.09 (m, 1H), 3.98 (dd, 1H), 3.20-3.02 (m, 3H), 2.99 (s, 3H), 2.87 (m, 1H), 2.85 (s, 3H), 2.74 (m, 1H), 1.55 (m, 2H), 0.70 (m, 1H), 0.67 (d, 3H), 0.41 (d, 3H)

Similarly prepared

#### Example 9

(2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC  $R_t$ =3.41 minutes,  $m/z$   $[M+H]^+ = 496$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.67 (dt, 1H), 7.59 (1H, d), 7.21-7.11 (m, 4H), 6.99-6.92 (m, 1H), 6.92-6.84 (m, 1H), 6.35 (d, 1H), 5.43 (s, 1H), 3.99 (dd, 1H), 3.93 (dd, 1H), 3.17-2.71 (m, 6H), 1.88-1.70 (m, 2H), 1.48-1.38 (m, 1H), 0.86 (s, 3H), 0.81-0.74 (m, 5H), 0.51-0.45 (m, 2H).

#### Example 10

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide:

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

A mixture of 2,4-difluorobenzaldehyde (1.421g), (D)-leucine methyl ester hydrochloride (1.817g), triethylamine (1.391ml) and methanol (20ml) was stirred at room temperature for 16 hours. N-tert-butoxycarbonyl-(D)-indanylglycine (2.914g) and 2-benzyloxyphenylisocyanide (2.090g) were then added sequentially. After 24 hours the solvent was

removed under reduced pressure and the reaction mixture was taken up in dichloromethane (ca. 20ml) and purified by Biotage<sup>TM</sup> flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:9 ethyl acetate:cyclohexane) to afford methyl (2R)-2-{[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (5.100g) (HPLC Rt = 4.40 minutes m/z [M+H]<sup>+</sup> = 770). This was taken up in 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was left at room temperature for 3 hours. The solvent and hydrogen chloride were blown off using a stream of nitrogen overnight. The crude material was taken up in methanol (90ml) containing triethylamine (10ml). After 30 minutes, the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by Biotage<sup>TM</sup> flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:2 ethyl acetate:cyclohexane) to yield (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g). HPLC Rt = 3.99 minutes, m/z [M+H]<sup>+</sup> = 638

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g) was dissolved in ethyl acetate (200ml) and hydrogenated at atmospheric pressure over 10% palladium on carbon catalyst (0.980g of 10% Pd/C:water 1:1 w/w) at room temperature for five hours. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to give the (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide as a cream-coloured foam (2.650g).

HPLC Rt = 3.61 minutes, m/z [M-H]<sup>-</sup> = 546 (no [M+H]<sup>+</sup> visible)

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid.

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.650g) was stirred in dichloromethane (20ml) and carbonyldiimidazole (1.178g) was added. the mixture was left at room temperature for 16 hours then the solvent was removed under reduced pressure. The residue was then taken up in 1:1 acetone:water (v/v) (80ml) and left at room temperature for 30 minutes. The bulk of the acetone was then removed under reduced pressure and the residue was partitioned between dichloromethane and 0.5M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated

under reduced pressure. The crude product was purified (Biotage<sup>TM</sup> flash chromatography column, 90g silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to afford (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid as a colourless solid 1.524g as a mixture of epimers.  
HPLC Rt = 3.44 and 3.58 minutes, both m/z [M+H]<sup>+</sup> = 457

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

The acid (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid (0.747g) prepared as described above was dried over P<sub>4</sub>O<sub>10</sub> in vacuo for five hours to give 0.724g drier material; this was dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 0.450g) and the mixture was sonicated for ca. 1 min to give a gelatinous mass. After 10 minutes at room temperature a solution of dimethylamine in tetrahydrofuran (10ml of 2M solution) was added to give a clear solution; this was left for 16 hours at room temperature. The solvents were removed under reduced pressure and the mixture was partitioned between dichloromethane and 0.1M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (12g Biotage<sup>TM</sup> silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to give the (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a colourless solid 0.285g.

HPLC Rt = 3.43 minutes, m/z [M+H]<sup>+</sup> = 484

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47–7.40 (m, 1H), 7.24–7.11 (m, 4H), 7.01–6.91 (m, 3H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19–3.01 (m, 3H), 2.99 (3, 3H), 2.92–2.75 (m, 5H), 1.64–1.51 (m, 2H), 0.76–0.66 (m, 4H), 0.43 (d, 3H).

## 35 Method 5

### Example 11

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid

R-Indanylglycine (1.91g) was suspended in dioxane (10ml) and water (10ml). To this was added triethylamine (1.7ml) and N-(benzyloxycarbonyloxy)succinimide (2.54g) and the reaction mixture was stirred rapidly at room temperature for 2 days. The reaction mixture was poured into water (50ml) and extracted with chloroform (100ml). The organic phase was washed with 1N hydrochloric acid (50ml) and water (50ml). This was dried over magnesium sulphate and the solvent removed *in vacuo* to give (2R)-

[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (3.06g).

HPLC Rt = 3.35 minutes; m/z [M+H]<sup>+</sup> = 326.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40-7.29 (m, 5H), 7.21-7.11 (m, 4H), 5.28 (d, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.14-2.79 (m, 5H).

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

To a solution of (D)-leucine methyl ester hydrochloride (1.45g) in methanol (10ml) was added triethylamine (1.12ml) and 2,4-difluorobenzaldehyde (0.875ml). The mixture was stirred for 3 days before (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (2.6g) and 2-benzyloxyphenylisocyanide (1.76g) were sequentially added. The reaction mixture was left to stand for 24 hours. The solvent was removed *in vacuo* and the residue was separated between ethyl acetate (200ml) and water (200ml). The organic phase was washed with brine. To this solution was added palladium on carbon (2.0g) and acetic acid (10ml) and the reaction mixture was stirred under an atmosphere of hydrogen for 2 hours. The mixture was filtered through Celite and washed with water (3x100ml), saturated sodium bicarbonate solution, brine and dried over magnesium sulphate. The solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane (50% to 66%) to give (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.0g). HPLC Rt = 3.59 minutes; m/z [M+H]<sup>+</sup> = 548.

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Carbonyldiimidazole (4.80g, 1.54 equiv.) was suspended in anhydrous dichloromethane (40mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (10.50g, pre-dried in vacuo over P<sub>4</sub>O<sub>10</sub> for 24 hours) was then added with stirring and the resultant solution was stirred at room temperature for 6 hours. The resulting yellow solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (54mL, 5.6 equiv.) and the resulting mixture was stirred at room temperature for 16 hours. The solvents plus residual dimethylamine were removed under reduced pressure and the reaction mixture was taken up in

dichloromethane (200mL) and washed with 1M hydrochloric acid (200mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to ca. 50mL. The crude product was applied to 4x90g silica Biotage™ columns on a Quad 3 system; each column being eluted with (i) 2:1 v/v ethyl acetate:cyclohexane (12x50mL fractions), (ii) ethyl acetate (12x50mL fractions), (iii) 9:1 v/v ethyl acetate:methanol to give (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (5.753g, 62%) as a colourless solid.

HPLC Rt = 3.41 minutes, m/z [M+H]<sup>+</sup> = 484

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48–7.38 (m, 2H), 7.24–7.11 (m, 4H), 7.01–6.90 (m, 2H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19–3.01 (m, 3H), 2.99 (s, 3H), 2.92–2.75 (m, 5H), 1.64–1.51 (m, 2H), 0.76–0.66 (m, 4H), 0.43 (d, 3H).

Similarly prepared:

#### Example 12

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide colourless solid, 41%

HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 470

#### Example 13

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide colourless solid, 36%

HPLC Rt = 3.3 minutes, m/z [M+H]<sup>+</sup> = 456

#### Example 14

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 61%

HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 526

#### Example 15

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid,

45%

HPLC Rt = 3.2 minutes, m/z [M+H]<sup>+</sup> = 512

(azetidin-3-ol prepared by the method of S S Chatterjee and D J Triggle; J Chem. Soc. Chem. Comm. (2) 93 (1968))

#### Example 16

(3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 46%

HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 496

**Example 17**

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide colourless solid, 59%

5 HPLC Rt = 3.3 minutes, m/z [M+H]<sup>+</sup> = 514

**Example 18**

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide colourless solid,

10 22%

HPLC Rt = 3.2 minutes, m/z [M+H]<sup>+</sup> = 576

**Example 19**

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide colourless solid, 11%

15 HPLC Rt = 3.5 minutes, m/z [M+H]<sup>+</sup> = 552

(2,2,2-trifluoroethylmethylamine hydrochloride was prepared by the method of E R Bissell and M Finger; J. Org. Chem. 24 1256-1259 (1959))

**Example 20**

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide tan foam, 19%

20 HPLC Rt = 3.5 minutes, m/z [M+H]<sup>+</sup> = 561

**Example 21**

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide

25 HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 500

**Example 22**

(2R)-2-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid

Carbonyldiimidazole (1.42g, 1.6 equiv.) was suspended in anhydrous dichloromethane (10mL) and the suspension was left at room temperature for 15 minutes. (2R)-2-(2,4-

35 difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (3.00g) was then added and the

resultant solution was stirred at room temperature for 16 hours. The resulting yellow solution was then evaporated under reduced pressure and the residue was treated with a 1:1(v/v) mixture of water and acetone (10 mL). The mixture was stirred for 2

40 hours, then the acetone was removed under reduced pressure and the residue was partitioned between dichloromethane and 0.1M HCl aq. The organic phase was separated using a hydrophobic frit then evaporated to low volume and purified by chromatography

on a Biotage Quad 3 system (90g silica column) eluted with 1:1(v/v) ethyl acetate:cyclohexane, then ethyl acetate, then 1:1 (v/v) ethyl acetate:methanol to give a mixture of diastereomers (2.61g). These were separated on a chiral reverse-phase column (Chiralcel OD, eluted with 15% propan-2-ol/heptane containing 0.1%TFA) to give:  
5 (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid (1.60g)  
HPLC Rt = 3.4 minutes, m/z [M+H]<sup>+</sup> = 457

### Example 23

10 methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate  
Carbonyldiimidazole (0.324g, 1.6 equiv.) was suspended in anhydrous dichloromethane (4mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-  
15 dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (0.800g) was then added with stirring and the resultant solution was left at room temperature for 16 hours. The mixture was then treated with methanol (10mL) and left at room temperature overnight. The solvents were removed under reduced pressure and the residue was purified by preparative plate chromatography on silica (20x20cm plates x4 eluted with 1:3 ethyl  
20 acetate:cyclohexane x5) to give: methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate (0.453g, 66%)  
HPLC Rt = 3.42 minutes, m/z [M+H]<sup>+</sup> = 471

Similarly prepared:

25

### Example 24

propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate  
HPLC Rt = 3.71 minutes, m/z [M+H]<sup>+</sup> = 499

30

### Example 25

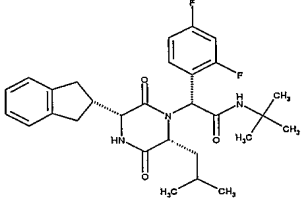
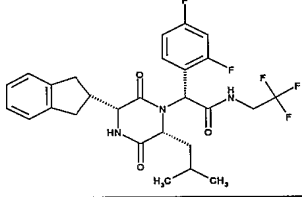
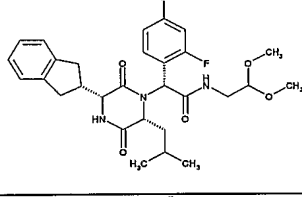
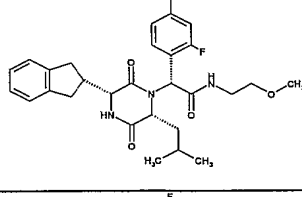
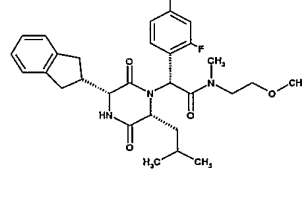
1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate  
(2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-  
35 dioxopiperazin-1-yl]ethanoic acid (example 22) (0.130g) was stirred in anhydrous DMF (1mL) and anhydrous potassium carbonate (0.020g, 0.5 eq.) was added. The mixture was stirred at room temperature for 1 hour then cooled to -10°C (ice-salt bath). The heterogeneous mixture was treated with 1-bromoethyl acetate (0.120mL, excess) and stirred for 3.5 hours keeping the bath temperature between -10 and -5°C. It was then  
40 partitioned between DCM and 1M HCl aq. (20 mL each). The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure to give a purple gum; this was purified by SPE cartridge (5g, silica eluted with (i) cyclohexane x2, (ii) DCM x2,

(iii) diethyl ether x2, (iv) ethyl acetate x2, (v) methanol x2 to give 1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate (0.081g) as a yellow foam.  
HPLC Rt = 3.5 minutes, m/z [M+H]<sup>+</sup> = 543

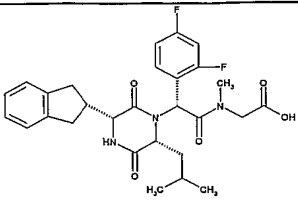
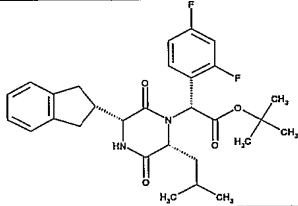
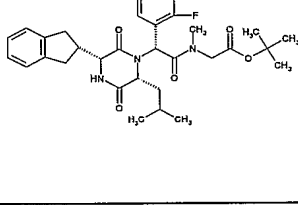
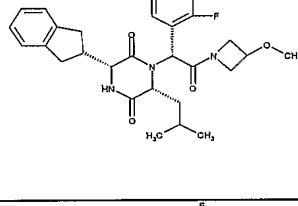
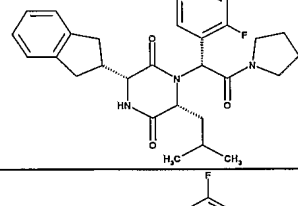
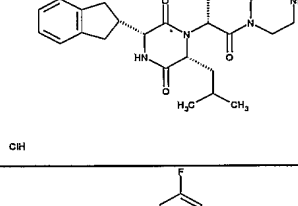
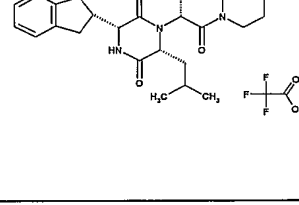
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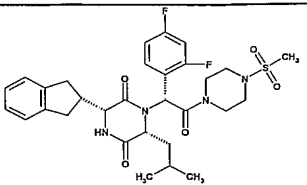
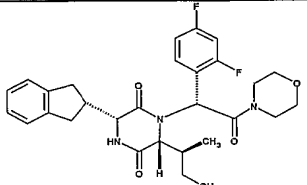
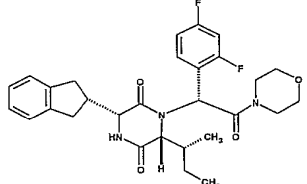
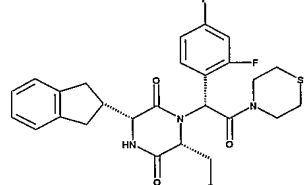
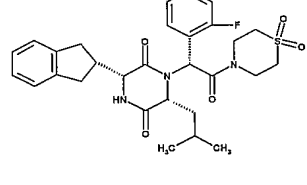
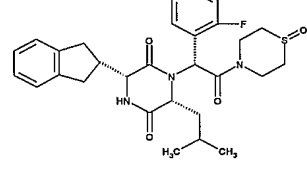
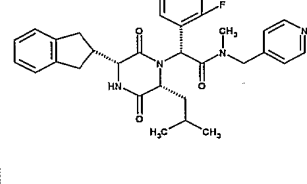
Similarly prepared:

10 In the table below, Examples 26, 54-55, 66-104, 107-117, 124-131 were prepared via method 1. The t-butyl ester Example 39 was prepared via perchloric acid-catalysed transesterification of the corresponding acid (Example 22) with t-butyl acetate by the procedure of T Kolasa and M J Miller; Journal of Organic Chemistry (1990), 55(6), 1711-21. Other Examples in the table below were prepared via method 5.

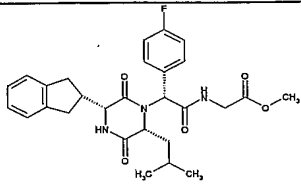
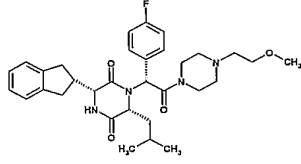
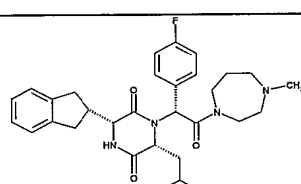
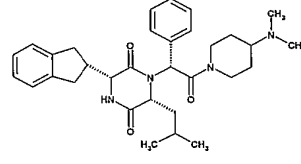
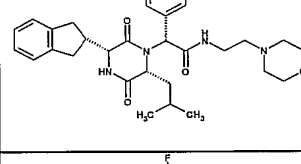
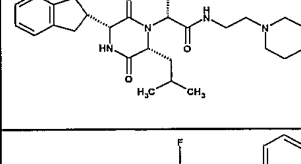
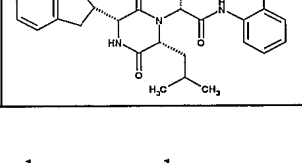
Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
26		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-((2,4-difluorophenyl)-2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl)ethanamide
27		537.5	3.4	538	536	(2R)-2-((2,4-difluorophenyl)-2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl)-N-(2,2,2-trifluoroethyl)ethanamide
28		543.6	3.2	544	542	(2R)-2-((2,4-difluorophenyl)-2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl)-N-(2,2-dimethoxyethyl)ethanamide
29		513.6	3.3	513	511	(2R)-2-((2,4-difluorophenyl)-2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl)-N-(2-methoxyethyl)ethanamide
30		527.6	3.4	528	none	(2R)-2-((2,4-difluorophenyl)-2-((3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl)-N-(2-methoxyethyl)-N-methylethanamide

31		571.7	3.3	572	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-bis(2-methoxyethyl)ethanamide
32		528.6	2.7	529	none	(2R)-2-(2,4-difluorophenyl)-N-[2-(dimethylamino)ethyl]-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N-methylethanamide
33		654.7	2.7	541	539	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-[2-(dimethylamino)ethyl]-N-methylethanamide trifluoroacetate
34		511.6	3.6	512	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-N-methylethanamide
35		471.6	3.2	472	470	(2R)-2-(2,4-difluorophenyl)-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N,N-dimethylethanamide
36		497.6	3.5	498	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-4-methyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
37		554.7	2.7	555	none	(2R)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-4-[2-(dimethylamino)ethyl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N,N-dimethylethanamide

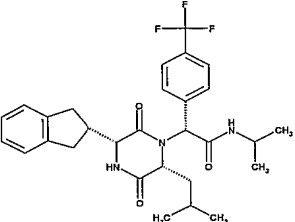
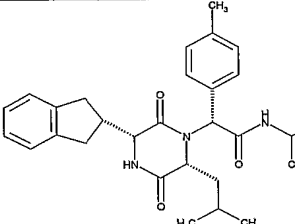
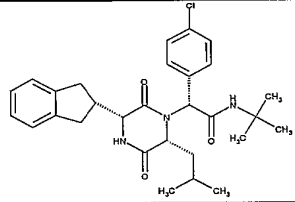
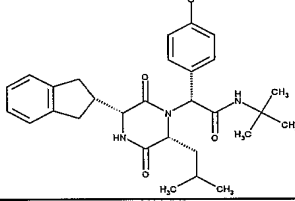
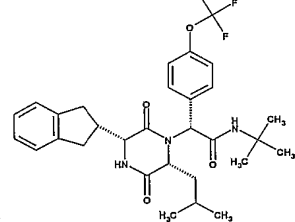
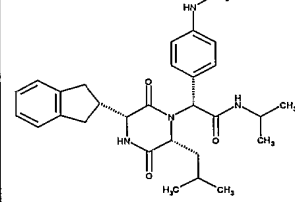
38		527.6	3.3	528	526	[{(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl}(methyl)amino]acetic acid
39		512.6	3.7	513	511	tert-butyl (2R)-2-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
40		583.7	3.6	584	none	tert-butyl [{(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl}(methyl)amino]acetate
41		525.6	3.3	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-methoxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
42		509.6	3.5	510	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-pyrrolidin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
43		561.1	2.7	525	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-piperazin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione hydrochloride
43a		652.7	2.7	539	583(M +45)	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione trifluoroacetate

44		602.7	3.3	603	601	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
45		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
46		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
47		541.7	3.6	542	540	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-thiomorpholin-4-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
48		573.7	3.3	574	572	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
49		557.7	3.1	558	556	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1-oxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
50		560.6	3	561	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-4-ylmethyl)ethanamide

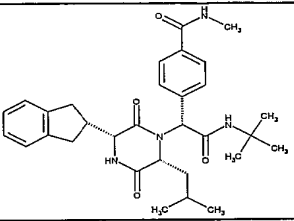
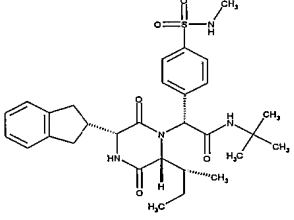
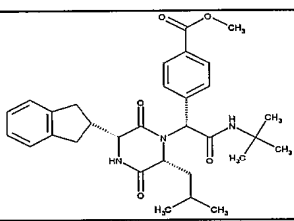
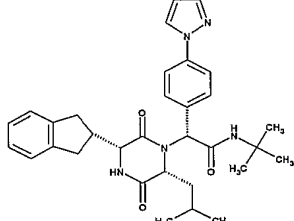
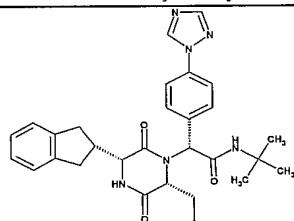
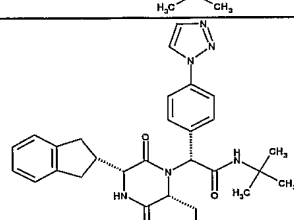
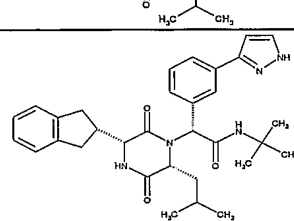
51		605.7	3.5	606	604	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
52		605.7	3.5	606	604	(2S)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
53		538.6	3.4	539	537	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(1,3-thiazol-2-yl)ethanamide
54		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
55		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
56		437.5	3.3	438	436	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide
57		481.6	3	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-hydroxyethyl)ethanamide
58		509.6	3.4	510	508	[(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide]

						fluorophenyl)ethanoyl](methyl)amino]acetic acid
59		509.6	3.4	510	508	methyl {[ (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanoyl]amino} acetate
60		564.7	2.6	565	563	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-{(1R)-1-(4-fluorophenyl)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethyl}-6-isobutylpiperazine-2,5-dione
61		534.7	2.6	535	533	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(4-fluorophenyl)-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
62		548.7	2.6	549	547	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-2-[4-(dimethylamino)piperidin-1-yl]-1-(4-fluorophenyl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
63		550.7	2.7	551	549	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-morpholin-4-ylethyl)ethanamide
64		548.7	2.8	549	547	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-piperidin-1-ylethyl)ethanamide
65		619.7	3.9	620	618	(2R)-N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide

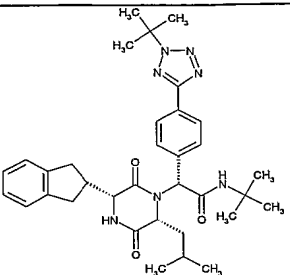
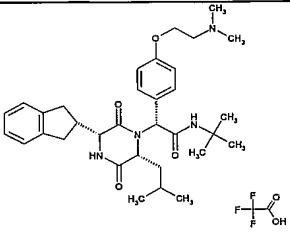
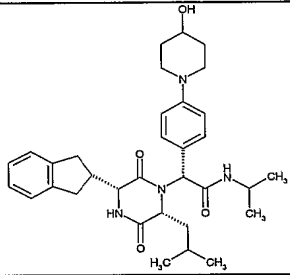
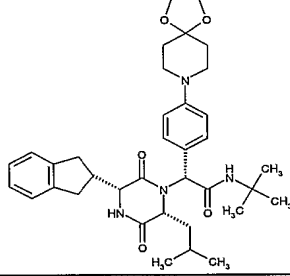
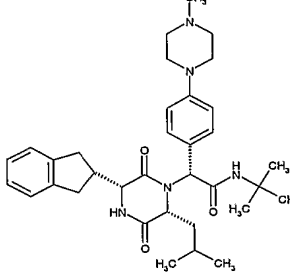
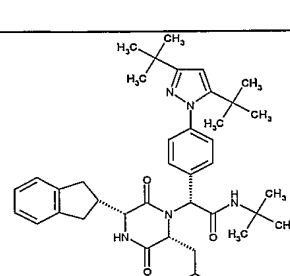
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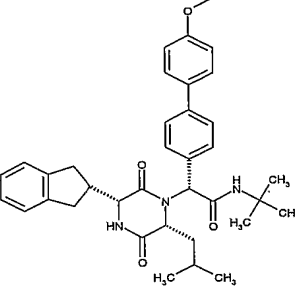
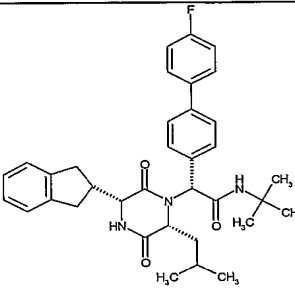
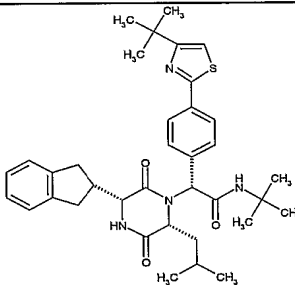
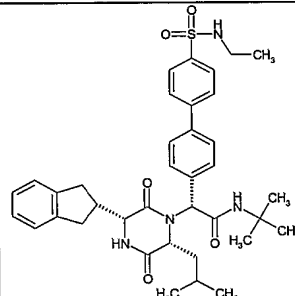
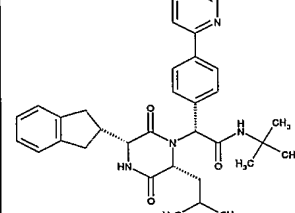
Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
66		529.6	3.8	530	528	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(trifluoromethyl)phenyl]ethanamide
67		475.6	3.6	476	474	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-methylphenyl)ethanamide
68		510.1	3.8	510	508	(2R)-N-(tert-butyl)-2-(4-chlorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
69		505.7	3.5	506	504	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-methoxyphenyl)ethanamide
70		559.7	3.8	560	558	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(trifluoromethoxy)phenyl]ethanamide
71		490.6	3.4	491	489	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylamino)phenyl]ethanamide

72		504.7	3.6	505	503	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)phenyl]-N-isopropylethanamide
73		530.7	3.7	553(M+Na)	529	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-pyrrolidin-1-ylphenyl)ethanamide
74		532.7	3.7	533	531	(2R)-2-[4-(diethylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
75		504.6	3.1	505	503	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]benzamide
76		518.6	3.0	519	517	(2R)-2-[4-(acetylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
77		532.7	3.2	533	531	(2R)-2-[3-(acetylamino)phenyl]-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
78		539.7	3.3	540	538	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylsulfonyl)phenyl]ethanamide

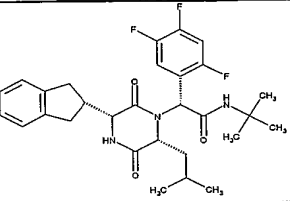
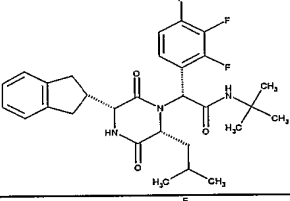
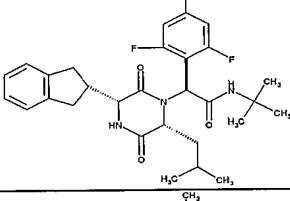
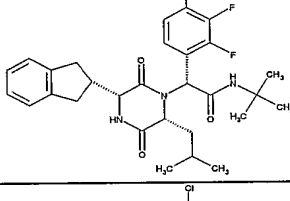
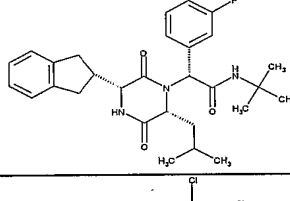
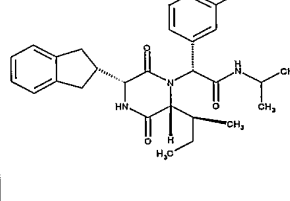
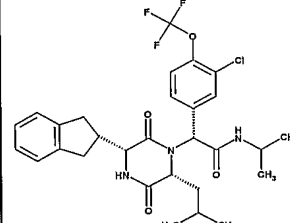
79		532.7	3.3	533	531	4-{(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl}-N-methylbenzamide
80		568.7	3.4	569	567	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-{4-[(methylamino)sulfonyl]phenyl}ethanamide
81		533.7	3.6	532	534	methyl 4-{(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl}benzoate
82		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-1-yl)phenyl]ethanamide
83		542.8	3.3	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,4-triazol-1-yl)phenyl]ethanamide
84		542.8	3.2	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,3-triazol-1-yl)phenyl]ethanamide
85		541.7	3.5	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-pyrazol-3-yl)phenyl]ethanamide

86		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-3-yl)phenyl]ethanamide
87		519.4	3.4	520	518	3-[(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl]phenylboronic acid
88		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-2-yl)phenyl]ethanamide
89		541.7	3.1	542.0	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-imidazol-1-yl)phenyl]ethanamide
90		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-1-yl)phenyl]ethanamide
91		560.8	3.4	561	559	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-morpholin-4-ylphenyl)ethanamide
92		541.7	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-4-yl)phenyl]ethanamide

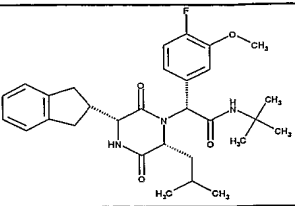
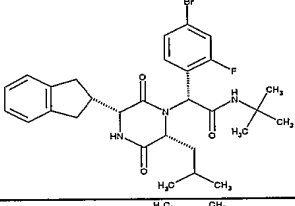
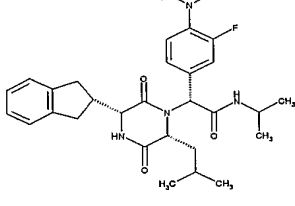
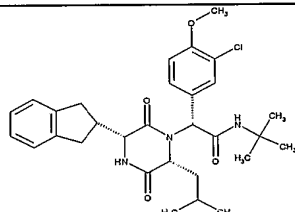
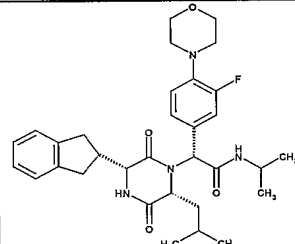
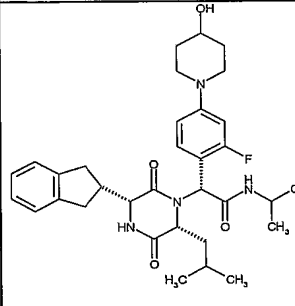
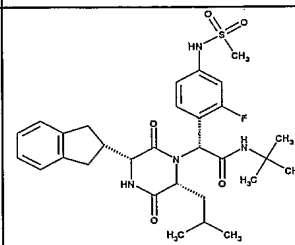
93		599.8	3.9	600	598	(2R)-N-(tert-butyl)-2-[4-(2-tert-butyl-2H-tetrazol-5-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
94		562.7	2.9	563	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4-[2-(dimethylamino)ethoxy]phenyl}ethanamide trifluoroacetate
95		560.8	3.0	561	559	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
96		616.9	3.5	617	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)phenyl]ethanamide
97		573.8	2.9	574	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]ethanamide
98		654.0	4.1	654	652	(2R)-N-(tert-butyl)-2-[4-(3,5-ditert-butyl-1H-pyrazol-1-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

99		581.7	4.0	582	580	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-methoxy-1,1'-biphenyl-4-yl)ethanamide
100		569.8	3.9	none	568	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-fluoro-1,1'-biphenyl-4-yl)ethanamide
101		614.8	4.3	615	613	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-tert-butyl-1,3-thiazol-2-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
102		658.9	3.6	659	657	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4'-[(ethylamino)sulfonyl]-1,1'-biphenyl-4-yl}ethanamide
103		552.8	3.6	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-2-ylphenyl)ethanamide

104		552.8	3.3	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-3-ylphenyl)ethanamide
105		522.7	2.4	523	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4-[(dimethylamino)methyl]-2-fluorophenyl}-N,N-dimethylethanamide
106		495.6	2.9	496	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(hydroxymethyl)phenyl]-N,N-dimethylethanamide
107			3.4	498	496	(2R)-2-(2,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
108			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
109			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
110			3.6	512	510	(2R)-N-(tert-butyl)-2-(2,3-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

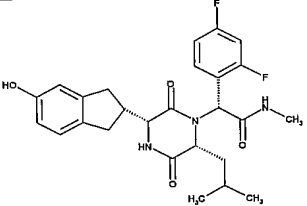
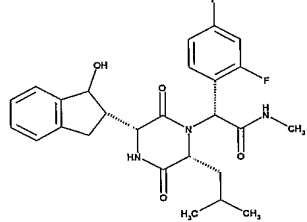
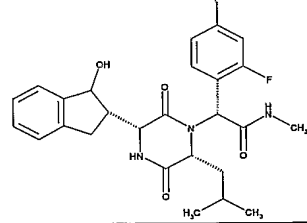
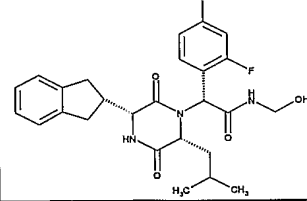
111			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,5-trifluorophenyl)ethanamide
112			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,3,4-trifluorophenyl)ethanamide
113			3.6	530	528	(2S)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,6-trifluorophenyl)ethanamide
114			3.8	526	524	(2R)-N-(tert-butyl)-2-(2,3-difluoro-4-methylphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
115			3.8	528	526	(2R)-N-(tert-butyl)-2-(4-chloro-3-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
116			3.7	530	528	(2R)-2-(3,4-dichlorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
117			3.7	580	578	(2R)-2-[3-chloro-4-(trifluoromethoxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

118			3.0	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-hydroxyphenyl)-N,N-dimethylethanamide
119			3.3	496	494	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isopropyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-N-isopropylethanamide
120			3.6	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-methoxyphenyl)ethanamide
121			3.1	540	538	{4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetic acid
122			3.6	596	594	tert-butyl {4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetate
123			3.3	553	none	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenyl dimethylcarbamate
124			3.5	none	552	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4,5-dimethoxyphenyl)ethanamide

125			3.7	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluoro-3-methoxyphenyl)ethanamide
126			3.8	none	570/572	(2R)-2-(4-bromo-2-fluorophenyl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
127			3.5	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)-3-fluorophenyl]-N-isopropylethanamide
128			3.7	540	538	(2R)-N-(tert-butyl)-2-(3-chloro-4-methoxyphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
129			3.3	565	563	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide
130			3.2	579	577	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
131			3.3	587	585	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{2-fluoro-4-[(methylsulfonyl)amino]phenyl}ethanamide

Hydroxylated metabolites of (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide were prepared as follows:

2 litres of growing cell cultures of *Streptomyces rimosus* BS33 was used to biotransform GW796679x. 500mg of GW796679X was added after 3 days growth and the broth harvested after another 5 days incubation. At harvest, 2 litres of methanol was added, then the cells removed by centrifugation. Methanol was removed from the supernatant by evaporation. The compounds were then extracted with ethyl acetate, evaporated to dryness, and purified by preparative HPLC to give examples 132,133,134 and 135.

132		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2S)-5-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N-methylethanamide
133		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-[(2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
134		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-[(2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
135		485.5	3.1	486	530(M+45)	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(hydroxymethyl)ethanamide

### Example 136

(2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

Benzofuran-5-carboxaldehyde (215 mg, 1.47 mmol) and D-leucine t-butyl ester hydrochloride (329 mg, 1.47 mmol) were dissolved in methanol (1.5ml) and triethylamine (0.205 ml, 1.47 mmol) added. The mixture, a pale yellow solution, was left to stand at room temperature overnight (23.5 hours). Then Boc-D-indanylglycine (429 mg, 1.47 mmol) was added followed by isopropylisocyanide (0.138 ml, 1.51 mmol). The mixture, a yellow solution, was left to stand at room temperature overnight (23.5 hours) before the solvent was evaporated under reduced pressure to leave a yellow gum. The gum was dissolved in 4M hydrogen chloride in dioxan (3 ml, 12 mmol) and left to stand at room temperature for 7.5 hours before it was evaporated under reduced pressure to leave an orange / brown gum. The gum was dissolved in methanol (2 ml) and 4M hydrogen chloride in dioxan (1 ml, 4 mmol) added. The mixture was left to stand at room temperature for 5.5 hours before the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (4ml) and triethylamine (0.5 ml, excess) added. The mixture was stirred at room temperature overnight (18.3 hours) before the solvent was removed by evaporation under reduced pressure. The residue was loaded in dichloromethane onto a SPE column (10g silica, Mega Bond Elut cartridge, pre-eluted with cyclohexane). The column was eluted stepwise (40 – 45 ml each step) with 100% chloroform, 3 : 1 cyclohexane : diethyl ether, 1 : 1 cyclohexane : diethyl ether, 1 : 3 cyclohexane : diethyl ether, 100% diethyl ether, 1 : 1 cyclohexane : ethyl acetate, 1 : 2 cyclohexane : ethyl acetate and 100% ethyl acetate. The 1 : 3 cyclohexane : diethyl ether to 1 : 2 cyclohexane : ethyl acetate fractions inclusive were combined to give a pale yellow solid (336 mg). The solid was loaded in dichloromethane onto 6 preparative chromatography plates (silica gel 60 plates, 20 × 20 cm<sup>2</sup>). The plates were eluted four times with 30 : 1 dichloromethane : isopropanol. The required band was extracted with 9 : 1 ethyl acetate : methanol to give (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide as a white solid (141mg, 0.28 mmol)

HPLC Rt = 3.46 minutes; m/z [M+H]<sup>+</sup> = 502.

<sup>1</sup>H NMR δ 7.95 (d, 1H), 7.73 (d, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.37 (dd, 1H), 7.16 (m, 4H), 6.79 (d, 1H), 5.79 (d, 1H), 5.37 (s, 1H), 4.11 (m, 1H), 4.03 (br dd, 1H), 3.99 (dd, 1H), 3.16-2.97 (m, 3H), 2.95-2.78 (m, 2H), 1.79(m, 1H), 1.69 (m, 1H), 1.33 (m, 1H), 1.09 (t, 6H), 0.78 (d, 3H), 0.67 (d, 3H).

Similarly prepared

### Example 137

(2R)-2-(1,2,3-benzothiadiazo-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.50 minutes; m/z [M+H]<sup>+</sup> = 534.

<sup>1</sup>H NMR δ 8.66 (d, 1H), 7.82 (d, 1H), 7.67 (dd, 1H), 7.20 (m, 4H), 6.72 (br d, 1H), 6.13 (s, 1H), 5.19 (s, 1H), 4.06 (br dd, 1H), 4.00 (dd, 1H), 3.18 (m, 1H), 3.07 (m, 2H), 2.92

(m, 1H), 2.81 (m, 1H), 1.86(m, 1H), 1.80 (m, 1H), 1.54 (m, 1H), 1.36 (s, 9H), 0.85 (d, 3H), 0.78 (d, 3H).

**Example 138**

5 (2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z [M+H]<sup>+</sup> = 504.

<sup>1</sup>H NMR δ 7.81 (br s, 1H), 7.18 (m, 5H), 6.79 (d, 1H), 6.44 (br d, 1H), 5.50 (d, 1H), 5.06 (s, 1H), 4.61 (t, 2H), 4.08 (m, 1H), 3.96 (m, 2H), 3.22 (t, 2H), 3.15 (m, 1H), 3.07 (d, 2H),  
10 2.90 (m, 1H), 2.79 (dd, 1H), 1.82(m, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.12 (dd, 6H), 0.83 (d, 3H), 0.77 (d, 3H).

**Example 139**

15 (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.48; m/z [M+H]<sup>+</sup> = 520

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.97 (d, 1H), 6.88 (dd, 1H), 6.82 (d, 1H), 6.58 (m, 1H), 6.06 (m, 2H), 5.64 (s, 1H), 5.02 (m, 1H), 3.95 (m, 2H), 3.16 (m, 1H), 3.07 (m, 2H), 2.89 (m, 1H), 2.77 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.32 (s, 9H), 0.83 (d, 3H), 0.79 (d, 3H)

**Example 140**

25 (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate

To a suspension of L-leucine (2.62g) in methanol (250ml) at -30°C under nitrogen was  
30 added a solution of benzofuran-5-carbaldehyde (2.92g) in methanol (15ml) and a suspension of 2-benzyloxyphenylisonitrile (4.19g) in methanol (15ml). The reaction was stirred at -30°C for 2 hours and then allowed to warm to room temperature and stirred for a further 3 days. The solvent was removed *in vacuo* and the residue was passed through a Biotage<sup>TM</sup> column (3x90g) eluting with cyclohexane: ethyl acetate (5:1) to afford after  
35 evaporation of the appropriate fractions methyl N-[(1R)-2-{[2(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.11g).

HPLC Rt=3.97 minutes, m/z [M+H]<sup>+</sup> = 499

Methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate

- 5 A mixture of palladium on carbon (10%, 500mg), methyl N-[(1R)-2-[(2-(benzyloxy)phenyl)amino]-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.1g) and ethyl acetate (60ml) was stirred under a hydrogen atmosphere for 5 hours. The reaction was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (3.429g).  
 10 HPLC Rt=3.49 min, m/z  $[M+H]^+ = 411$

Methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

- 15 A solution of methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (410mg) and 1,1'-thiocarbonyldiimidazole (196mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (20ml) was added to the reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide  
 20 (TBTU, 710mg) and a solution of dimethylamine in tetrahydrofuran (3ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was then passed down an SPE (5g, silica) eluting with a gradient (3:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (140mg).  
 25 HPLC Rt = 2.70 minutes m/z  $[M+H]^+ = 347$

N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

- To a solution of methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (520mg) in methanol (5ml) was added a solution of lithium hydroxide (91mg) in water (3ml). After stirring vigorously for 24 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid. This solution was applied to an Oasis<sup>TM</sup> cartridge (2x6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg).  
 35 HPLC Rt = 2.27 minutes m/z  $[M+H]^+ = 333$

(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

- 40 To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (419mg) in dry tetrahydrofuran (5ml) at -20°C under a nitrogen atmosphere was

added N-methylmorpholine (158µl) and a solution of isopropylchloroformate in toluene (1.0M, 1.44ml). After 10 minutes, a solution of N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg) in dimethylformamide (5ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (13ml) was added and the reaction was left to stand for a further 18 hours. The solvent was then removed *in vacuo* and the residue was separated between dichloromethane and saturated sodium bicarbonate solution. The organic phase was evaporated *in vacuo* and the residue was applied to an SPE (10g, silica). The product was eluted using an ethyl acetate: methanol gradient (3:1 to 1:3) to afford (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (51mg).

HPLC Rt=3.36 minutes, m/z [M+H]<sup>+</sup> = 488

<sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.47 (d, 1H), 8.07 (d, 1H), 7.71 (m, 1H), 7.69 (d, 1H), 7.38 (dd, 1H), 7.21 (m, 2H), 7.12 (m, 2H), 7.03 (m, 1H), 6.47 (s, 1H), 3.88 (m, 1H), 3.69 (dd, 1H), 3.07-2.67 (m, 5H), 2.87 (s, 3H), 2.77 (s, 3H), 1.40-1.70 (m, 2H), 0.46 (m, 1H), 0.42 (d, 3H), 0.02 (d, 3H)

#### Example 141

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

(2RS)-2-(2-methyl-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

A mixture of 2-methyl-5-formylbenzofuran (1.26g), (D)-leucine methyl ester hydrochloride (1.57g), triethylamine (1.2ml) and methanol (20ml) was stirred at room temperature for 6 hours and then left to stand for 19 hours. N-benzylcarbonyl-(D)-indanylglycine (2.80g) and 2-benzyloxy-phenylisocyanide (1.89g) were then added sequentially and the mixture stirred for 2 days. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. This was washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine. The organic phase was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100ml) and acetic acid (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (1.5g). After 4 hours the catalyst was removed by filtration through a pad of celite and washed with dichloromethane/methanol (500ml of 1:1 v/v). The filtrate and washings were combined, evaporated under reduced pressure. The residue was separated between ethyl acetate and water. The organic phase was washed with water, saturated sodium bicarbonate solution and brine. The organic phase was dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was applied to a silica cartridge (100g) and eluted with cyclohexane/ethyl acetate (500ml of 3:1, 2:1, 1:1 v/v) and ethyl acetate (500ml). The required fractions were combined and evaporated

*in vacuo* to give (2RS)-2-(2-methylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (1.58g). HPLC Rt = 3.60 minutes; m/z [M+H]<sup>+</sup> = 566.

5     (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

Carbonyldiimidazole (92mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (5mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2-methylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.06mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to a silica cartridge (10g). This was eluted with cyclohexane (100ml), cyclohexane/ethyl acetate (100ml of 2:1, 3:2, 1:1, 2:3 and 1:2 v/v), ethyl acetate (200ml) and ethyl acetate/methanol (100ml of 19:1 v/v). The required fractions were combined and evaporated *in vacuo* to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide as an off-white solid (88mg).

HPLC Rt = 3.40 minutes; m/z [M+H]<sup>+</sup> = 502.

25     <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.52 (d, 1H), 7.43 (d, 1H), 7.27-7.13 (m, 5H), 6.54 (s, 1H), 6.38 (m, 1H), 6.31 (d, 1H), 4.24 (m, 1H), 3.99 (dd, 1H), 3.22-3.05 (m, 3H), 2.99 (s, 3H), 2.86 (m, 1H), 2.82 (s, 3H), 2.75 (m, 1H), 2.48 (m, 3H), 1.45 (m, 1H), 1.36 (m, 1H), 0.57 (m, 1H), 0.51 (d, 3H), 0.19 (d, 3H).

30     Similarly prepared: -

**Example 142**

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

35     HPLC Rt = 3.40 minutes; m/z [M+H]<sup>+</sup> = 516.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.57 (m, 1H), 7.41 (d, 1H), 7.28-7.11 (m, 5H), 6.61 (m, 1H), 6.37 (m, 1H), 5.49 (d, 1H), 5.23 (s, 1H), 4.11 (m, 1H), 4.02-3.93 (m, 2H), 3.19-3.05 (m, 3H), 2.92 (m, 1H), 2.77 (m, 1H), 2.48 (m, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.38 (m, 1H), 1.10 (m, 6H), 0.78 (d, 3H), 0.69 (d, 3H).

40

**Example 143**

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione

HPLC Rt = 3.38 minutes; m/z [M+H]<sup>+</sup> = 544.

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.51 (d, 1H), 7.45 (d, 1H), 7.26-7.14 (m, 5H), 6.57 (s, 1H), 6.39 (m, 1H), 6.34 (m, 1H), 4.20 (m, 1H), 3.99 (m, 1H), 3.73-3.33 (6H), 3.22-3.03 (m, 5H), 2.88 (m, 1H), 2.75 (m, 1H), 2.49 (m, 3H), 1.45 (m, 1H), 1.37 (m, 1H), 0.54 (m, 1H), 0.51 (d, 3H), 0.20 (d, 3H).

10 **Example 144**

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide

HPLC Rt = 3.39 minutes; m/z [M+H]<sup>+</sup> = 505.

- 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56 (d, 1H), 7.45 (d, 1H), 7.32 (dd, 1H), 7.23 (m, 2H), 7.16 (m, 2H), 6.55 (s, 1H), 6.23 (d, 1H), 5.89 (d, 1H), 4.22 (m, 1H), 3.99 (dd, 1H), 3.21-3.04 (m, 3H), 3.00 (s, 3H), 2.87 (m, 1H), 2.84 (s, 3H), 2.75 (m, 1H), 1.47 (m, 1H), 1.38 (m, 1H), 0.58-0.49 (m, 4H), 0.22 (d, 3H).

5-Bromo-2-fluoro-1-benzofuran

- 20 5-Bromobenzofuran-2-carboxylic acid (4.68g) was suspended in carbon tetrachloride (150ml) and water (50ml). To this was added sodium bicarbonate (3.36g), followed by Selectflor (7.1g) and the reaction mixture was stirred rapidly for 20 hours. The reaction mixture was diluted with dichloromethane and 2N sodium hydroxide solution. The organic phase was separated, washed with brine and dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure at room temperature. The residue was applied to a silica cartridge (20g) and eluted with diethyl ether. This gave 5-bromo-2-fluoro-1-benzofuran (1.4g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.61 (d, 1H), 7.36 (dd, 1H), 7.26 (d, 1H), 5.84 (dd, 1H).

30 2-Fluoro-5-formyl-1-benzofuran

- A slurry of magnesium powder (219mg) and iodine (cat) in dry tetrahydrofuran (3ml) was heated at 50°C under nitrogen for 20 minutes. 5-Bromo-2-fluoro-1-benzofuran (1.4g) was dissolved in dry tetrahydrofuran (6ml). A 1ml portion of the solution was added to the slurry at 50°C without stirring. After 30 minutes the rest of the solution was added slowly and the reaction was heated at reflux for 3 hours. The reaction was cooled in an ice/water bath and dimethylformamide (1ml) was added dropwise maintaining the temperature below 10°C. After 1 hour a mixture of 2N hydrochloric acid (12.5ml) and brine (12.5ml) was added. The reaction mixture was extracted using ethyl acetate (3x25ml). The combined organics were washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed in vacuo and the residue applied to a silica cartridge (50g). This was eluted with cyclohexane, cyclohexane/ethyl acetate (6:1, 5:1 v/v). This gave 2-fluoro-5-formyl-1-benzofuran (376mg).
- 40

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.05 (s, 1H), 8.04 (m, 1H), 7.83 (dd, 1H), 7.54 (d, 1H), 6.01 (dd, 1H).

**Example 145**

5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide

HPLC Rt = 3.42 minutes; m/z [M+H]<sup>+</sup> = 520.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.61 (d, 1H), 7.42 (d, 1H), 7.31 (dd, 1H), 7.21 (m, 2H), 7.16 (m, 2H), 6.70 (d, 1H), 5.89 (d, 1H), 5.57 (d, 1H), 5.18 (s, 1H), 4.11 (m, 1H), 3.98 (m, 2H), 3.16 (m, 1H), 3.08 (m, 2H), 2.91 (m, 1H), 2.78 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.41 (m, 1H), 1.12 (d, 3H), 1.10 (d, 3H), 0.81 (d, 3H), 0.72 (d, 3H).

**Example 146**

15 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione

HPLC Rt = 3.35 minutes; m/z [M+H]<sup>+</sup> = 548.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (d, 1H), 7.47 (d, 1H), 7.31 (dd, 1H), 7.27-7.14 (m, 4H), 6.58 (s, 1H), 6.38 (d, 1H), 5.91 (d, 1H), 4.19 (m, 1H), 4.00 (dd, 1H), 3.73-3.50 (m, 5H), 3.39 (m, 1H), 3.23-3.04 (m, 5H), 2.87 (m, 1H), 2.76 (m, 1H), 1.47 (m, 1H), 1.40 (m, 1H), 0.53 (d, 3H), 0.51 (m, 1H), 0.24 (d, 3H).

**Example 147**

25 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide

HPLC Rt = 3.38 minutes; m/z [M+H]<sup>+</sup> = 487.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.03 (s, 1H), 7.66 (d, 1H), 7.49 (d, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 7.18-7.10 (m, 4H), 7.02 (m, 1H), 6.57 (s, 1H), 6.55 (m, 1H), 4.29 (m, 1H), 4.00 (dd, 1H), 3.22-3.03 (m, 3H), 3.00 (s, 3H), 2.92-2.73 (m, 5H), 1.40 (m, 1H), 1.33 (m, 1H), 0.57 (m, 1H), 0.45 (d, 3H), 0.06 (d, 3H).

**Example 148**

30 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-methyl-N-[2-(methylsulphonyl)ethyl]ethanamide

HPLC Rt = 3.20 minutes; m/z [M+H]<sup>+</sup> = 579.

35 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.62 (s, 1H), 7.64 (d, 1H), 7.41 (d, 1H), 7.30 (m, 1H), 7.26-7.10 (m, 6H), 6.51 (m, 1H), 6.48 (s, 1H), 4.18 (m, 1H), 4.05-3.90 (m, 2H), 3.68-3.50 (m, 2H), 3.28-3.01 (m, 4H), 2.96-2.69 (m, 8H), 1.41 (m, 2H), 0.65 (m, 1H), 0.47 (d, 3H), -0.10 (d, 3H).

**Example 149**

40 (2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

- 5 A mixture of 5-formylbenzothiophene (2.0g), (D)-leucine methyl ester hydrochloride (2.24g), triethylamine (1.72ml) and methanol (20ml) was stirred at room temperature for 24 hours. N-*tert*-butoxycarbonyl-(D)-indanylglycine (3.59g) and 2-benzyloxy-phenylisocyanide (2.58g) were then added sequentially and the mixture stirred for 4 days. Then the solvent was removed under reduced pressure. The residue was taken up in  
 10 dichloromethane (20ml) and 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was stirred at room temperature for 2 hours. The solvent and hydrogen chloride were evaporated under reduced pressure. The crude material was dissolved in dichloromethane (30ml) and triethylamine (10ml) added. The mixture was stirred for 18  
 15 hours before the dichloromethane and excess of triethylamine were removed under reduced pressure. The crude product was dissolved in dichloromethane (100ml) and washed with 1N hydrochloric acid (2x100ml) and brine. The organic phase was dried over MgSO<sub>4</sub> and evaporated *in vacuo* to yield (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide as a brown foam (7.5g).  
 20 HPLC Rt = 3.88 minutes, m/z [M+H]<sup>+</sup> = 658.

(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

- 25 (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (1.0g) was dissolved in dichloromethane (5ml) and to this was added dropwise a 1.0M solution of BBr<sub>3</sub> in dichloromethane (2.0ml). The reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture was added 1N hydrochloric acid (30ml) and  
 30 dichloromethane (20ml). The phases were separated and the organic phase was washed with 1N hydrochloric acid (30ml) and brine (30ml). The organic phase was dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The residue was purified by Biotage<sup>TM</sup> flash column chromatography, eluting with 3:2 ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-  
 35 hydroxyphenyl)ethanamide (210mg).

HPLC Rt = 3.55 minutes, m/z [M+H]<sup>+</sup> = 568.

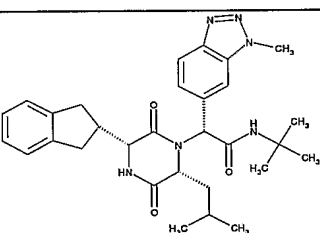
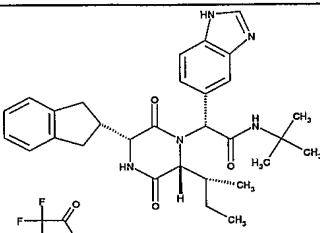
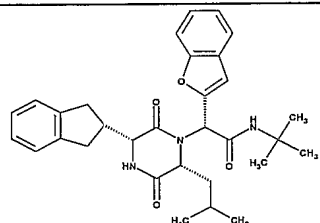
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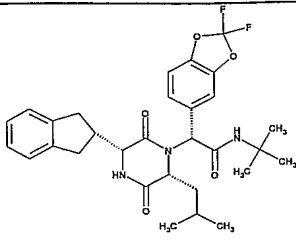
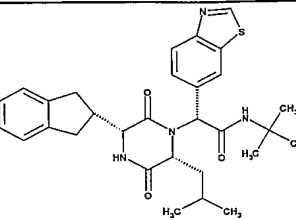
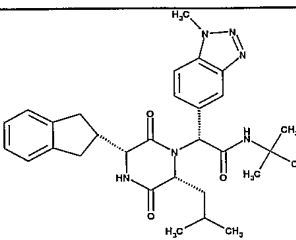
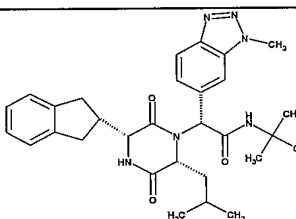
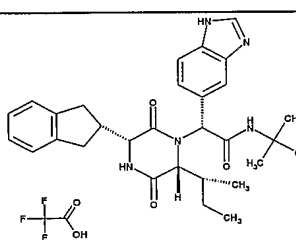
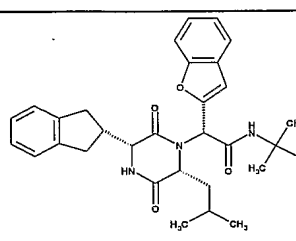
Carbonyldiimidazole (100mg) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. 2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.0mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was evaporated under reduced pressure. The crude product was purified by silica column chromatography eluting with 1:1v/v ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2R)-2-(benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a white solid (90mg).

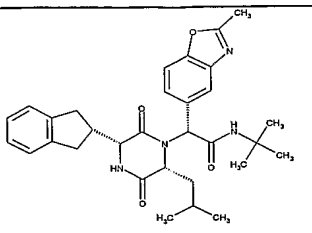
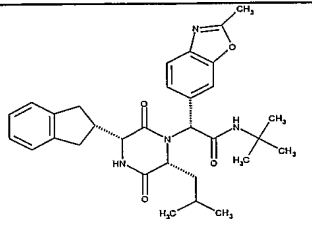
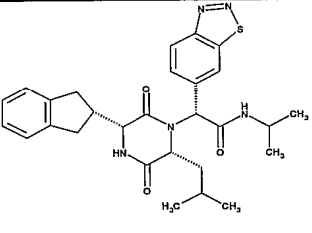
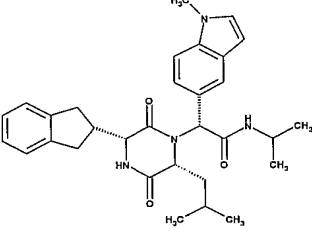
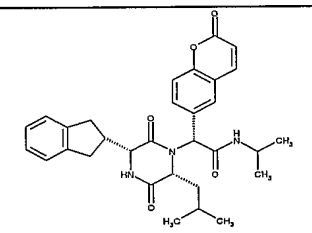
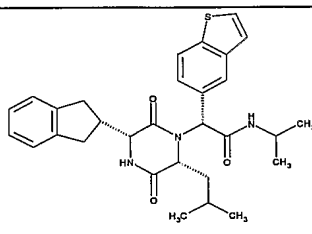
HPLC Rt = 3.35 minutes, m/z [M+H]<sup>+</sup> = 504.

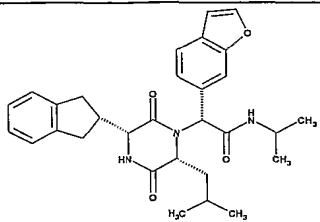
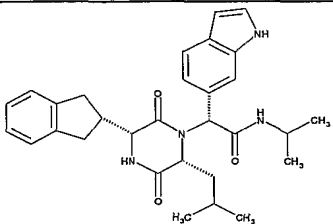
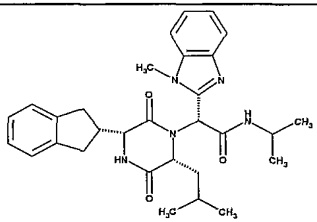
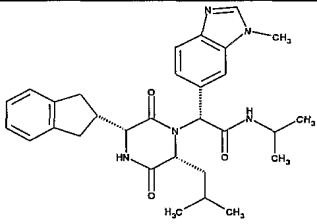
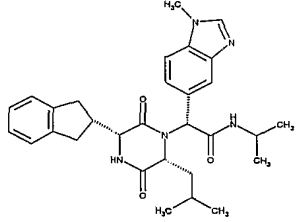
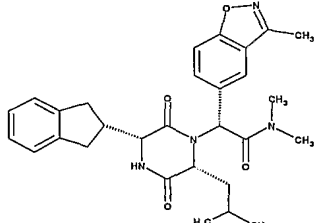
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.94 (d, 1H), 7.89 (m, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.41 (m, 1H), 7.35 (d, 1H), 7.23 (m, 1H), 7.13 (m, 3H), 6.63 (s, 1H), 4.25 (m, 1H), 4.02 (dd, 1H), 3.23-3.04 (m, 3H), 3.01 (s, 3H), 2.93-2.77 (m, 5H), 1.50-1.32 (m, 2H), 0.52 (m, 1H), 0.49 (d, 3H), 0.12 (d, 3H).

Compounds 150-169 and 174-175 were prepared via method 1. Compound 170 was prepared via method 2. Compounds 171, 172 and 173 were prepared via method 5.

No.	Regno	MWt	Rt/min	MH +	MH -	Name
150		517.7	3.62	518	516	(2R)-N-(tert-butyl)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
151		516.6	3.12	517	515	2-(1H-1,2,3-benzotriazol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]acetamide
152		533.7	3.42	534		(2R)-N-(tert-butyl)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

153		555.6	3.71	556	554	(2R)-N-(tert-butyl)-2-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
154		532.7	3.32	533	531	(2R)-2-(1,3-benzothiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
155		530.7	3.18	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-5-yl)ethanamide
156		530.7	3.22	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-6-yl)ethanamide
157		629.7	3.06		514	(2R)-2-(1H-benzimidazol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide trifluoroacetate
158		515.7	3.72	516	514	(2R)-2-(1-benzofuran-2-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

159		530.7	3.3	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-5-yl)ethanamide
160		530.7	3.35	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-6-yl)ethanamide
161		519.7	3.37	520	518	(2R)-2-(1,2,3-benzothiadiazol-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
162		514.7	3.41	515		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-indol-5-yl)ethanamide
163		529.6				(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-oxo-2H-chromen-6-yl)ethanamide
164		517.7	3.53	518	516	(2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

165		501.6	3.42	502	500	(2R)-2-(1-benzofuran-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
166		500.6	3.35	501	499	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-isopropylethanamide
167		515.7	4.88	516	514	2R-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-2-yl)acetamide
168		515.7	4.32	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-6-yl)ethanamide
169		515.7	2.65	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-5-yl)ethanamide
170		502.6	3.35	503	501	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(3-methyl-1,2-benzisoxazol-5-yl)ethanamide

171		486.6	3.07	487	485	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-5-yl)-N,N-dimethylethanamide
172		487.6	2.94	488		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-5-yl)-N,N-dimethylethanamide
173		487.6	2.99	488	486	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-6-yl)-N,N-dimethylethanamide
174		511.7	3.56	512		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-naphthyl)acetamide
175		512.7	3.19	513		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-quinolin-6-ylacetamide

**Example 176**

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

5

To a solution of 5-trifluoromethyl-furan-2-carbaldehyde (140mg)[prepared as in ref. Chem. Heterocycl. Compd. 13, 1977, 1280-1282 by R.V.Grigorash, V.V.Lyalin, L.A.Alekseeva and L.M.Yagupol'skii: 5-Trifluoromethylfuran Derivatives] in methanol

(1.1ml) was added triethylamine (118  $\mu$ l) and (D)-leucine t-butyl ester hydrochloride (190mg). The mixture was left to stand for 16.33 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (246mg) and isopropylisocyanide (77.4 $\mu$ l) were sequentially added. The mixture, a yellow solution, was left to stand for 24 hours before the solvent was removed *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane (3ml) and left to stand for 6.75 hours at ambient temperature. After this time, the solvent was removed *in vacuo*. The residue was dissolved in methanol (4ml) and treated with a solution of 4M hydrogen chloride in dioxane (0.2ml) and was left to stand overnight. After this time, the solvent was removed *in vacuo*. The residue was stirred in dioxane (9.5ml) containing triethylamine (0.5ml) and dichloromethane (5ml) for 4.75 hours. Then the mixture was evaporated *in vacuo* to leave a light brown solid. This crude material was purified by SPE column (10g, silica Mega Bond Elut<sup>TM</sup>) eluting stepwise with 100% chloroform, 4:1 cyclohexane : diethyl ether, 3:1 cyclohexane : diethyl ether, 2:1 cyclohexane : diethyl ether, 1:1 cyclohexane : diethyl ether, 1:2 cyclohexane : diethyl ether, 1:3 cyclohexane : diethyl ether, 100% diethyl ether, 1:1 ethyl acetate : cyclohexane, 2:1 ethyl acetate : cyclohexane, 3:1 ethyl acetate : cyclohexane, 100% ethyl acetate. The 1:2 cyclohexane : diethyl ether to 2:1 ethyl acetate : cyclohexane fractions inclusive were combined to give an orange gum (215mg). The gum was purified further, to separate the isomers, by preparative plate chromatography. Whatman PK6F silicagel 60 plates 20  $\times$  20 cm<sup>2</sup>, eluted in 1:1 ethyl acetate : cyclohexane six times and extracted with 9:1 ethyl acetate : methanol to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide (64mg), HPLC Rt = 3.59 minutes; m/z [M+H]<sup>+</sup> = 520.

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.88 (d, 1H), 7.16 (m, 4H), 6.85 (d, 1H), 6.74 (d, 1H), 6.30 (d, 1H), 5.73 (s, H), 4.19 (dd, 1H), 4.08 (m, 1H), 3.97 (dd, 1H), 3.14 (m, 2H), 3.01 (m, 1H), 2.84 (m, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.15 (d, 6H), 1.11 (m, 1H), 0.82 (dd, 6H).

Similarly prepared

#### Example 177

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide

By the procedure of Example 176 but using 5-methyl-thiophene-2-carbaldehyde

HPLC Rt = 3.46 minutes; m/z [M+H]<sup>+</sup> = 482.

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.21 (m, 2H), 7.16 (m, 2H), 6.94 (d, 1H), 6.67 (d, 1H), 6.63 (d, 1H), 5.73 (d, 1H), 4.94 (s, 1H), 4.07 (m, 1H), 3.93 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.93 (m, 1H), 2.77 (m, 1H), 2.47 (s, 3H), 1.96 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.17 (d, 3H), 1.12 (d, 3H), 0.94 (d, 3H), 0.92 (d, 3H)

**Example 178**

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

5 N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide

A mixture of 5-trifluoromethyl-furan-2-carbaldehyde (351mg), (D)-leucine methyl ester hydrochloride (389mg), triethylamine (0.298ml) and methanol (2.2ml) was stirred at room temperature for 4 hours and then left to stand for 19 hours. N-*tert*-butoxycarbonyl-  
 10 (D)-indanylglycine (623mg) and 2-benzyloxy-phenylisocyanide (448mg) were then added sequentially and the mixture stirred for 7 hours before being left to stand at room temperature for 41 hours. Then the solvent was removed under reduced pressure to leave an orange / brown syrup. This was taken up in 4M hydrogen chloride in 1,4-dioxane (2.8ml) and the mixture was stirred at room temperature for 2 hours. The solvent and  
 15 hydrogen chloride were evaporated under reduced pressure. The crude material was dissolved in methanol (5ml) and triethylamine (0.54ml) added. The mixture was stirred for 18 hours before the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by Biotage<sup>TM</sup> flash column chromatography (40g silica cartridge eluted with 1:5 ethyl acetate:cyclohexane (600ml),  
 20 1:3 ethyl acetate:cyclohexane (400ml) and 1:2 ethyl acetate:cyclohexane (450ml)) to yield N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide as an orange solid (472mg).

25 HPLC Rt = 4.04 minutes, m/z [M+H]<sup>+</sup> = 660.

2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide

30 N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide (469mg) was dissolved in ethyl acetate (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (100mg). After 4 hours the catalyst was removed by filtration through glass fibre filters and washed with ethyl acetate. The filtrate and washings were  
 35 combined, evaporated under reduced pressure and dried *in vacuo* at room temperature to leave a yellow / brown solid (400mg). The solid was dried over P<sub>2</sub>O<sub>5</sub> overnight to give 2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide (365mg).  
 HPLC Rt = 3.64 minutes, m/z [M+H]<sup>+</sup> = 570.

40

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

Carbonyldiimidazole (78mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. (R)-N-(2-Hydroxy-phenyl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(5-trifluoromethyl-furan-2-yl)-acetamide (172mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (0.9mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to 3 preparative chromatography plates, which were eluted with 1:1v/v ethyl acetate:cyclohexane. The required band was extracted with ethyl acetate to give the (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide as a pale yellow solid (87mg).  
HPLC Rt = 3.51 minutes, m/z [M+H]<sup>+</sup> = 506.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.19 (m, 5H), 6.86 (dd, 1H), 6.64 (d, 1H), 6.61 (s, 1H), 4.25 (m, 1H), 3.97 (dd, 1H), 3.20-3.02 (m, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 2.88 (m, 1H), 2.80 (m, 1H), 1.70 (m, 1H), 1.67 (m, 1H), 0.74 (d, 3H), 0.70 (m, 1H), 0.63 (d, 3H).

#### Example 179

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

By the procedure of Example 178, using (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

HPLC: Rt = 2.88 minutes ; m/z (M+H)<sup>+</sup> = 453

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

A mixture of 2-methyl-oxazole-4-carbaldehyde<sup>(1)</sup> (340mg), (D)-leucine methyl ester hydrochloride (568mg), triethylamine (0.435ml) and anhydrous methanol (20ml) was stirred at room temperature for 18 hours. N-benzyloxycarbonyl-(D)-indanylglycine (1.015g) and 2-benzyloxy-phenylisocyanide (648mg) were then added sequentially and the mixture stirred for 12 days before being left to stand at room temperature for 10 days. The solvent was removed under reduced pressure to leave a dark orange gum which was dissolved in ethyl acetate (150mL) and washed with 2M hydrochloric acid (100mL), saturated sodium bicarbonate solution (100mL) and saturated sodium chloride solution (50mL) then dried over anhydrous magnesium sulphate and concentrated under reduced pressure to a volume of 5mL. This crude solution was diluted with ethanol (80mL)

containing acetic acid (1.6mL) and added under vacuum to 10% palladium on carbon (50% water, 425mg). The resulting suspension was stirred under an atmosphere of hydrogen for 20 hours, filtered (celite filteraid) washed with ethanol (50mL) and the filtrate added under vacuum to a second quantity of 10% palladium on carbon (50% water, 670mg). The suspension was stirred under an atmosphere of hydrogen for 2 hours, the hydrogenation apparatus was then evacuated and refilled with hydrogen and the suspension stirred for a further 20 hours. The suspension was filtered (celite filteraid) washed with ethanol (200mL) and the combined filtrates concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate solution (100mL) and dichloromethane (60mL), then the organic layer dried (hydrophobic frit) and the solvent removed under reduced pressure. Purification by Biotage flash chromatography (40g silica) eluting with ethyl acetate : cyclohexane (3:1, 300mL) ethyl acetate (300mL) then ethyl acetate : methanol (20:1, 600mL) gave (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide as a brown foam (197mg).  
 HPLC : Rt = 3.28 minutes ; m/z (M+H)<sup>+</sup> = 517  
 Ref (1) CAS 113732-84-6

**Example 180**

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione  
 By the procedure of Example 179, using morpholine  
 HPLC: Rt = 2.89 minutes ; m/z (M+H)<sup>+</sup> = 495

**Example 181**

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide  
 By the procedure of Example 180, using 5-methyl-thiophene -2-carbaldehyde  
 HPLC Rt = 3.25 minutes; m/z M<sup>+</sup> = 468.

**Example 182**

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide  
 By the procedure of Example 178, using 3-fluoro-5-methyl-thiophene-2-carbaldehyde  
 HPLC: Rt = 3.20 minutes ; m/z M<sup>+</sup> = 486

2-(3-Bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane

3-Bromo-5-methyl-2-thiophenecarbaldehyde (1.00g) was dissolved in dry 1,4-dioxane (8ml). Molecular sieves (4 Angstrom, 2g), 1,3-propandiol (9ml), p-toluene sulphonic acid (362mg) were added and the mixture was stirred under a nitrogen atmosphere, at room temperature, over night. Molecular sieves were removed by filtration and the filtrate evaporated. The residue was taken up with ethyl acetate and washed with

saturated solution of sodium carbonate. The aqueous was extracted with more ethyl acetate and the combined layers washed with brine, dried over magnesium sulphate, filtrated and concentrated to a yellow oil (1g).

- 5 Purification was performed by filtration on a SPE cartridge (Silica-10g) using dichloromethane as eluent. The solution was eventually concentrated to yield 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane as a yellow solid (1.18g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400MHz): 6.60ppm (s, 1H); 5.72ppm (s, 1H); 4.23ppm (m, 2H); 3.98ppm (m, 2H); 2.44ppm (d, 3H); 2.22ppm (m, 1H); 1.42ppm (m, 1H).

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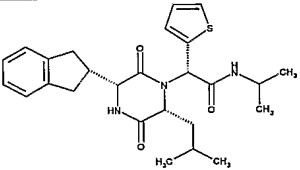
### 3-Fluoro-5-methyl-thiophene-2-carbaldehyde

- To a solution of 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane (1.16g) in dry tetrahydrofuran (10ml), under a nitrogen atmosphere, at -78 °C, 1.6M *n*-butyl lithium in hexane (3.30ml) was added dropwise. After 15 minutes stirring, N-fluoro-benzene-sulfonyl-imide (1.66g) was added portionwise. The solution was stirred at -78 °C for further 10 minutes, allowed to warm to room temperature and then stirred for a further 60 minutes. The reaction was quenched with water (5ml), diluted with diethyl ether (20ml) and washed with 1N sodium hydroxide (30ml). The aqueous was extracted with diethyl ether again (2x10ml), the combined organic layers were dried over magnesium sulphate, 20 filtrated and evaporated. The residue was redissolved in 1,4-dioxane (15ml) and water (10), *p*-toluene sulphonic acid (837mg) was added and the solution was stirred at room temperature, over night. Neutralised with a saturated solution of sodium bicarbonate (10ml), then extracted with ether twice. The organic was dried over magnesium sulphate and evaporated at reduced pressure (200mbar). The residual dioxane was removed by 25 distillation at reduced pressure, the residue further purified by flash chromatography (petroleum ether / dichloromethane 55/45), giving 3-fluoro-5-methyl-thiophene-2-carbaldehyde as a colourless oil (366mg), approximately 70% pure.

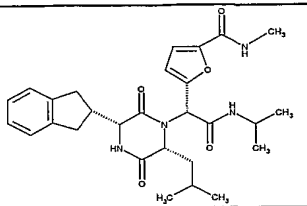
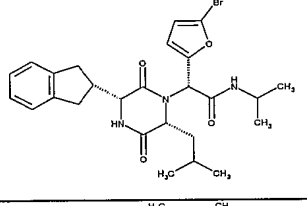
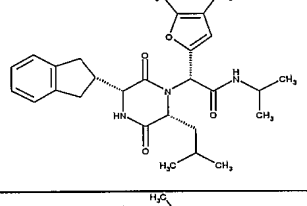
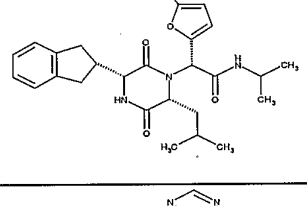
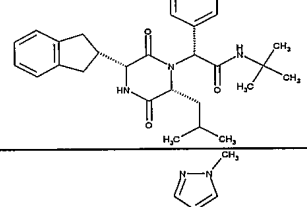
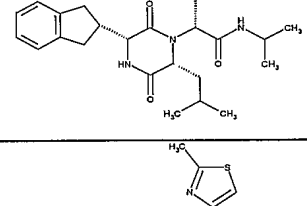
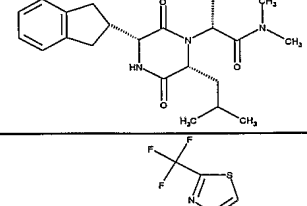
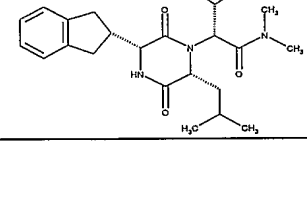
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400MHz): δ 9.93ppm (s, 1H); 6.62ppm (s, 1H); 2.52ppm (m, 3H).

- 30 Similarly prepared:

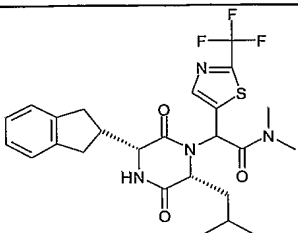
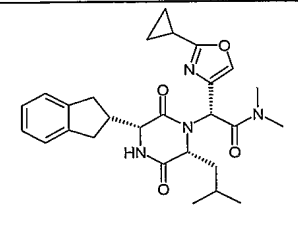
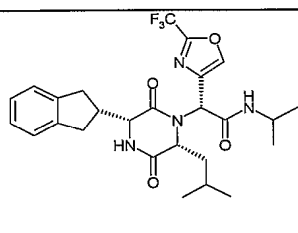
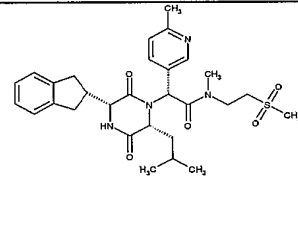
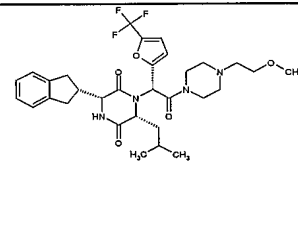
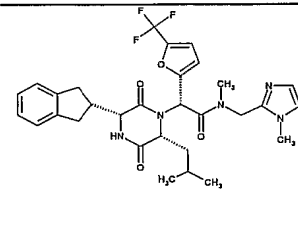
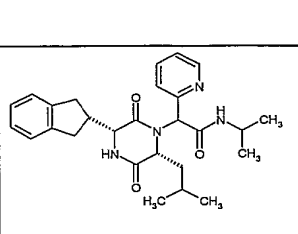
Compounds 183 -206,213,215,218,222-225 were prepared via method 1. Compounds 207,208,216, were prepared via method 2. Compounds 209-212, 214,217,219-221 and 226 were prepared via method 5.

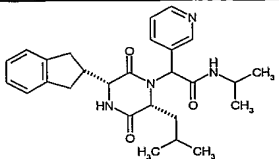
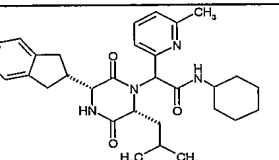
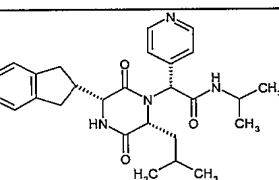
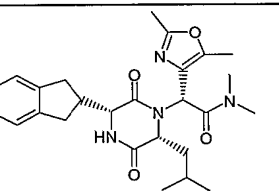
Eg No.	Structure	MWt	Rt /min	+ve ion	-ve ion	name
183		467.7	3.4	468	466	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-2-ylethanamide

184		546.6	3.6	546/5 48	546/5 44	(2S)-2-(5-bromothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
185		546.6	3.6	546/5 48	544/5 46	(2S)-2-(4-bromothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
186		502.1	3.6	501-3	499- 501	(2S)-2-(5-chlorothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
187		467.7	3.3	468	466	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-3-ylethanamide
188		544.8	3.4	545	543	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-pyridin-2-ylthien-2-yl)ethanamide
189		451.6	3.3	452	450	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-furyl)-N-isopropylethanamide
190		465.7	3.4	466	464	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-furyl)ethanamide
200		508.7	2.9	509	507	5-[1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-3-furamide

201		508.7	3	509	507	5-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-2-furamide
202		530.5	3.5	529/5 31	527/5 29	(2R)-2-(5-bromo-2-furyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
203		479.7	3.5	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4,5-dimethyl-2-furyl)-N-isopropylethanamide
204		465.7	3.4	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methyl-2-furyl)ethanamide
205		477.6	3.3	478	476	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-pyrimidin-5-ylethanamide
206		465.7	2.9	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-pyrazol-4-yl)ethanamide
207		468.7	3	469	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-thiazol-4-yl)ethanamide
208		522.6	3.4	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-4-yl]ethanamide

209		462.7	3.1	463	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-methylpyridin-3-yl)ethanamide
210		558.7	3.3	559	557	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-2-morpholin-4-yl-2-oxo-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl]piperazine-2,5-dione
211		464.6	2.7	465	463	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-oxo-1,6-dihydropyridin-3-yl)ethanamide
212		478.6	3.04	479.23	477.26	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(6-methoxypyridin-3-yl)-N,N-dimethylethanamide
213		479.6	3.03	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-dimethyl-1H-pyrazol-5-yl)-N-isopropylethanamide
214		466.56	3.1	467	-	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-ethyl-1,3-oxazol-4-yl)-N,N-dimethylethanamide
215		482.6	3.58	483	481	N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-thiazol-2-yl)acetamide

216		522.6	3.46	523	521	2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-5-yl]acetamide
217		478.6	3.07	479	477	(2R)-2-(2-cyclopropyl-1,3-oxazol-4-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
218		520.5	3.47	521	519	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[2-(trifluoromethyl)-1,3-oxazol-4-yl]ethanamide
219		554.7	2.8	555	553	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-2-(6-methylpyridin-3-yl)-N-[2-(methylsulfonyl)ethyl]ethanamide
220		604.7	2.7	605	603	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxo-1-[5-(trifluoromethyl)-2-furyl]ethyl]piperazine-2,5-dione
221		585.6	2.8	586	584	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[(1-methyl-1H-imidazol-2-yl)methyl]-2-[5-(trifluoromethyl)-2-furyl]ethanamide
222		462.6	3.29	463	461	2-[(3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl]-N-isopropyl-2-pyridin-2-ylacetamide

223		462.6	3.09	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-3-yl-acetamide
224		516.7	3.41	517	515	N-Cyclohexyl-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(6-methyl-pyridin-2-yl)-acetamide
225		462.6	2.93	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-4-yl-acetamide
226		466.6	3.06	467	-	(R)-2-(2,5-Dimethyl-oxazol-4-yl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N,N-dimethylacetamide

**Example 227**

(3R,6R)-1-[(1R)-1-(2,4-Difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

The azetidinol (Example 15) (57 mg) in anhydrous dichloromethane (2 mL) was stirred at  $-5^{\circ}\text{C}$  and diethylaminosulfur trifluoride (50  $\mu\text{L}$ , excess) was added in one portion. The mixture was left at room temperature overnight and saturated aqueous sodium hydrogen carbonate (3 mL) was added. The mixture was diluted with dichloromethane (10 mL) and the organic phase was separated using a hydrophobic frit and blown down with nitrogen. The crude reaction mixture was purified using the mass-directed autoprep system to give (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione (26 mg) as a white solid.

HPLC  $R_t$  = 3.34 minutes,  $m/z$   $[M+H]^+ = 514$

*Pharmacy Examples**Tablets*

5	a)	Compound of the invention	50.0mg
		Lactose	70.0mg
		Microcrystalline Cellulose	70.0mg
		Cross-linked polyvinylpyrrolidone	8.0mg
		Magnesium Stearate	<u>2.0mg</u>
		Compression weight	200.0mg

10 The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

15	b)	Compound of the invention	50.0mg
		Lactose	120.0mg
		Pregelatinised Starch	20.0mg
		Cross-linked polyvinylpyrrolidone	8.0mg
		Magnesium Stearate	<u>2.0mg</u>
		Compression weight	200.0mg

20 The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Capsules

25	a)	Compound of the invention	50.0mg
		Lactose	148.0mg
		Magnesium Stearate	<u>2.0mg</u>
		Fill weight	200.0mg

30 The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

35	b)	Compound of the invention	50.0mg
		Lactose	132.0mg
		Polyvinylpyrrolidone	8.0mg
		Cross-linked polyvinylpyrrolidone	8.0mg

Magnesium Stearate	<u>2.0mg</u>
Fill weight	200.0mg

5 The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

#### Injection Formulation

		% w/v
10	Compound of the invention	0.10
	Water for injections B.P. to	100.00

15 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Solubilisers, such as cosolvents, may also be added to facilitate solution of the compound of the invention. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the pH remeasured and adjusted if necessary, to provide 1mg/ml of the compound of formula (I).

20 The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

30 Further sterile formulations are prepared in a similar manner containing 0.05, 0.20 and 0.5% w/v of the compound of the invention, so as to provide respectively 0.5, 2 and 5mg/ml of the compound of the invention.

#### 35 Measurement of Oxytocin Antagonist Activity

Assay Buffer used throughout the assay: 50mM HEPES, 10mM MgCl<sub>2</sub>, 0.125mg/ml BSA, pH adjusted to 7.4 with KOH.

hOT-CHO membranes were prepared at a concentration of 0.3mg protein/ml in assay buffer. Test compounds were initially dissolved in DMSO (to 10mM) and diluted in DMSO (Beckman Biomek FX). 1µl of compound was transferred to black 384 assay plates (NUNC) using a Biomek FX. 20µl of 1nM Bodipy TMR Oxytocin (Perkin Elmer) in assay buffer was added to all wells (Labsystems Multidrop) then 20µl membrane added to all wells (Multidrop). Plates were incubated at room temp for 60 min.

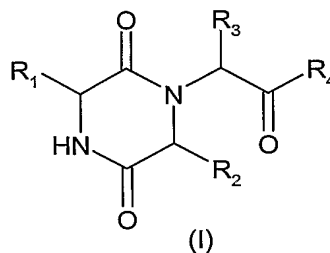
Polarisation was read on LJJ Analyst ( $\lambda_{Ex}=535nm$ ,  $\lambda_{Em}=580nm$ ,  $\lambda_{Dichroic}=555nm$ ). Data were fitted to a 4 parameter logistic equation. An estimated  $K_i$  was calculated as  $IC_{50}/5$ .

In the above test compounds of formula (I) in general have a  $pK_i$  value within the range of 7 to 11. Thus the compounds of examples 1 to 227 have a  $pK_i$  within the range 8.5 to 10.8.

The compounds of formula (I) are essentially non toxic at therapeutically active doses. Thus compound of the example 10 has been administered to rats at doses of up to 300mg/kg p.o for 4 days. and no adverse toxicological effects were observed.

## Claims

1. A method of treating or preventing benign prostatic hyperplasia which comprises  
5 administering to a mammal in need thereof of an effective amount of a compound of the  
formula (I)

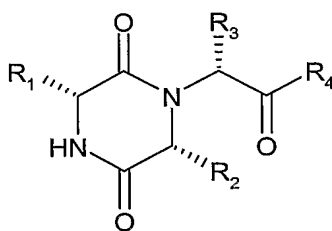


and/or a physiologically acceptable derivative thereof, wherein:

- 10 R<sub>1</sub> represents aryl (C<sub>1-4</sub>) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;  
R<sub>2</sub> represents C<sub>1-6</sub>alkyl (optionally substituted by a C<sub>1-2</sub>alkoxy, C<sub>1-2</sub>alkylthio, di(C<sub>1-2</sub>alkyl) amino or a C<sub>3-6</sub>cycloalkyl group) or C<sub>3-6</sub>cycloalkyl, or 5-6 membered heterocyclic group  
15 containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;  
R<sub>3</sub> represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused  
20 rings is benzene;  
R<sub>4</sub> represents OH or OC<sub>1-4</sub> alkyl (optionally substituted with C<sub>1-4</sub>alkylcarbonyloxy) or NR<sub>5</sub>R<sub>6</sub>;  
R<sub>5</sub> represents hydrogen, C<sub>1-6</sub>alkyl (optionally substituted with C<sub>1-4</sub>alkoxy) or C<sub>3-7</sub>cycloalkyl;  
25 R<sub>6</sub> represents hydrogen, methyl, C<sub>1-4</sub>alkoxy, C<sub>3-7</sub>cycloalkyl, C<sub>2-4</sub>alkyl [optionally substituted with one or more groups selected from: carboxyl, C<sub>1-4</sub>alkylsulphonyl, or C<sub>1-4</sub>alkoxycarbonyl], C<sub>2-4</sub>alkyl [optionally substituted with one or more groups selected from halogen, hydroxy, C<sub>1-4</sub>alkoxy or NR<sub>7</sub>R<sub>8</sub> wherein R<sub>7</sub> and R<sub>8</sub> independently represent hydrogen or C<sub>1-4</sub>alkyl or together with the nitrogen atom to which they are attached to  
30 form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from C<sub>1-3</sub>alkyl, hydroxy, C<sub>1-3</sub>alkoxy (optionally substituted by C<sub>3-6</sub>cycloalkyl or optionally substituted phenyl), C<sub>3-6</sub>cycloalkyl or NR<sub>c</sub>R<sub>d</sub> wherein R<sub>c</sub> and R<sub>d</sub> each independently represent a group selected from C<sub>1-3</sub>alkyl (optionally substituted by C<sub>3-6</sub>cycloalkyl or optionally substituted phenyl) or C<sub>3-6</sub>cycloalkyl)] or R<sub>6</sub> represents a  
35 phenyl or benzyl group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C<sub>3-7</sub>

cycloalkyl or the group  $\text{CH}_2\text{CONR}_9\text{R}_{10}$  wherein  $\text{R}_9$  represents hydrogen or  $\text{C}_{1-4}$ alkyl,  $\text{R}_{10}$  represents hydrogen,  $\text{C}_{1-4}$ alkyl optionally substituted by a 5 or 6 membered heteroaryl group or  $\text{R}_9, \text{R}_{10}$  and the nitrogen atom to which they are attached together form a 5 or 6 membered saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a  $\text{C}_{1-4}$ alkyl or  $\text{C}_{1-4}$ alkanoyl group; or  $\text{R}_5$  and  $\text{R}_6$  together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g.  $\text{SO}_2$  and the additional nitrogen atom either carries a hydrogen atom or a  $\text{C}_{1-4}$ alkyl or a  $\text{C}_{1-4}$ alkanoyl group or a  $\text{C}_{1-4}$ alkylsulphonyl group or a  $\text{C}_{1-3}$  alkoxy $\text{C}_{2-4}$  alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from  $\text{C}_{1-3}$ alkyl, hydroxy, oxo,  $\text{C}_{3-6}$ cycloalkyl or  $\text{NR}_e\text{R}_f$  wherein  $\text{R}_e$  and  $\text{R}_f$  each independently represent a group selected from  $\text{C}_{1-3}$ alkyl (optionally substituted by  $\text{C}_{3-6}$  cycloalkyl or optionally substituted phenyl) or  $\text{C}_{3-6}$  cycloalkyl.].

2. A method as claimed in claim 1 wherein  $\text{R}_1$  is a 2-indanyl group and  $\text{R}_2, \text{R}_3$  and  $\text{R}_4$  have the meanings defined in claim 1.
3. A method as claimed in claim 1 or claim 2 wherein  $\text{R}_4$  is hydroxy or the group  $\text{NR}_5\text{R}_6$ .
4. A method as claimed in any of claims 1 to 3 wherein the compounds have the stereochemistry as defined in formula (1a).



(1a)

wherein the groups  $\text{R}_1, \text{R}_2, \text{R}_3$  and  $\text{R}_4$  have the meanings defined for formula (I).

5. A method as claimed in any of claims 1 to 4 wherein  $\text{R}_2$  is a group selected from 1-methylpropyl or 2-methylpropyl.
6. A method as claimed in any of claims 1 to 5 wherein  $\text{R}_3$  is an optionally substituted phenyl group.

7. A method as claimed in any of claims 1 to 6 wherein R<sub>3</sub> is a 5 or 6 membered hetero aryl group.

8. A method as claimed in any of claims 1 to 7 wherein R<sub>3</sub> is a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene.

9. A method as claimed in any of claims 1 to 8 wherein R<sub>3</sub> is a group selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-

thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-indol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

10. A method as claimed in any of claims 1 to 9 wherein  $R_5$  is a group selected from hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy $C_{2-4}$ alkyl and  $R_6$  is a group selected from hydrogen,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyl substituted by 1 to 3 halogen atoms,  $C_{1-4}$ alkyl substituted by alkoxy, alkyl substituted by alkoxy, alkyl substituted by hydroxy, alkyl substituted by dialkylamino, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroaryl, methyl, heteroaryl, alkyl substituted by  $NR_7R_8$  wherein  $NR_7R_8$  form a 6-membered heterocyclic ring, cycloalkyl, or  $NR_5R_6$  represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring, thiomorpholino or the sulphoxide or sulphone thereof.

11. A method as claimed in any of claims 1 to 10 wherein the compound of formula (I) is selected from:-

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide  
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide  
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-morpholinamide  
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.  
 (2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.  
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.  
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.  
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

- (2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
- 5 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- 10 (3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
- 15 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
- 20 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
- 25 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
- methyl (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- propyl (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- 30 1-(acetyloxy)ethyl (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- 35 (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
- 40 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide
- 5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide
- (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
- 10 (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
- 15 (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- 20 (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.
- 25 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
- (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
- 30 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide
- 35 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide
- (2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
- 40

12. A pharmaceutical composition comprising a compound of formula (1) as defined in claim 1 or claim 2 together with one or more pharmaceutically acceptable carriers.

13. The use of compound of formula (1) as defined in claim 1 for the manufacture of  
5 a medicament for treating benign prostatic hyperplasia

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/006815

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/495 A61K31/496 A61P13/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/053443 A (HATLEY RICHARD JONATHAN ; LIVERMORE DAVID GEORGE HUBERT (GB); MILLER N) 3 July 2003 (2003-07-03)	12
P,Y	claims; examples	1-13
Y	EP 0 614 894 A (MERCK & CO INC) 14 September 1994 (1994-09-14) page 16, lines 25-34	1-13
X	WO 99/47549 A (ONTOGEN CORP) 23 September 1999 (1999-09-23) claims 1,7,17	12
A	US 5 817 751 A (SZARDENINGS ANNA KATRIN ET AL) 6 October 1998 (1998-10-06) column 1, lines 25-30; figure 2; examples	12
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

13 October 2004

Date of mailing of the international search report

28/10/2004

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Veronese, A

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/006815

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/03054 A (LXR BIOTECHNOLOGY INC ; TOMEI L DAVID (US)) 2 February 1995 (1995-02-02) the whole document -----	1-13
A	WO 03/033487 A (SCHERING CORP) 24 April 2003 (2003-04-24) claims 1,22 -----	1-13
Y	NICHOLSON H D ET AL: "Oxytocin and prostatic function." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY. 1995, vol. 395, 1995, pages 529-538, XP008036862 ISSN: 0065-2598 cited in the application abstract page 536, last paragraph -----	1-13

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/006815

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT



Information on patent family members

International Application No

PCT/EP2004/006815

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